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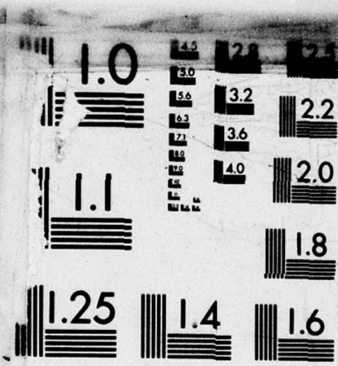

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ANNUAL PROGRESS REPORT

by

Robert W. Caldwell
Clinton B. Nash

July 1976
(For the period - July 1975 - 30 June 1976)

Supported by

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During this contract year, we have equipped and organized our laboratory for the measurement of pulmonary and cardiovascular function of dogs and performed studies with the candidate antimalarial, mefloquinine methanesulfonate. An Interim Report No. 1 deals with the acute effects of low dose-rates of mefloquine; while the latter report deals with the acute effects of high dose-rates of mefloquine.

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Mefloquine methanesulfonate (WR-142,490•CH_3SO_3H), when infused at a dose -rate of 1 mg/kg/min for 20 minutes in the anesthetized dog, caused either little or no effect on the pulmonary and cardiovascular parameters measured during this drug infusion or in the following 3 hour observation period. However, dose-rates of 2 and 3 mg/kg/min of mefloquine MS for 20 minutes did produce pulmonary and cardiovascular changes. The respiratory parameters which were observed to change were: 1) tidal volume, which fell during the drug infusion but then returned to control values during the remaining portion of the observation period; 2) respiratory rate, which rose during the drug infusion but returned to control levels; 3) dynamic airways resistance, which fell during drug administration but then rose above control levels and 4) small gradual changes in blood pO_2 and pCO_2. The cardiovascular parameters observed to change were: 1) arterial blood pressure, which fell during the drug infusion but returned rapidly to control levels; 2) cardiac contractile force, which fell during the drug infusion and returned toward control levels later in the observation period; 3) central venous pressure, which rose transiently during drug administration; 4) pulmonary artery pressure, which rose initially but tended to fall late in the observation period and 5) pulmonary wedge pressure, a measure of left atrial pressure, which rose and was maintained throughout the 3 hour observation period but which returned to control levels within a 24 hour period. The magnitude of the effects of mefloquine MS appeared to be more dependent on the dose-rate of drug delivery than on the total dose delivered.

-pO2

High dose-rate infusion of mefloquine MS of 8 or 10 mg/kg/min, by the i.v. route, produced a dramatic drop in blood pressure, heart rate and tidal volume and equally marked elevations in respiratory rate and pulmonary artery pressure. Pulmonary wedge pressure was also slightly elevated. Pulmonary compliance and resistance could not be accurately assessed during much of the drug infusion because of the marked reduction of tidal volume, but compliance appeared to increase slightly before death while the immediate effects of this infusion dose-rate on resistance was a reduction. While both the respiratory and cardiovascular systems failed and appeared to be involved in the death of the animal, cessation of breathing appeared to occur first. A Cheyne-Stokes breathing pattern (a crescendo-decrescendo pattern) was noted in several of the spontaneously breathing high dose-rate dogs. High dose-rates of 8 to 10 mg/kg/min of mefloquine MS can be lethal to dogs (55 to 80 mg - total dose), with respiration ceasing before the cardiovascular system fails.

pCO2

INTRODUCTION

Among the antiparasitic compounds, the antimalarial compounds that have been developed are quite varied in their chemical structure. Their effects on pulmonary and cardiovascular function have been found to be as dissimilar as their structure. Examples of this diversity are numerous. Aviado et al. (1970) have demonstrated a striking bronchodilatation following treatment with the 4aminoquinolines. Aviado (1967) also noted a potentiation of the cardiovascular effects of epinephrine by pretreatment of animals with sulfones. This unusual effect was also observed by Caldwell et al. (1972) following the administration of a sulfonylquinazoline. The production of a profound diuresis has been observed following administration of the pteridines (Aviado et al., 1968).

Effects of the antimalarial chemicals on heart rhythm have also been widely studied and reported. Arrhythmic and antiarrhythmic effects of chloroquine and analogs have been observed by a number of investigators (Hess and Schmidt, 1959; DiPalma, 1960; Don Michael and Awazzadeh, 1970; Caldwell and Hutchinson, 1971). The antiarrhythmic properties of quinidine are certainly well known and antiarrhythmic action of quinetholate, another quinine analog, have also been recently noted (Aviado et al., 1970; Nash et al., 1972).

All of these examples illustrate the need for observing the respiratory, cardiovascular and electrocardial effects of new antiparasitic compounds during preclinical testing. These "side effects" may frequently be noxious but, on the other hand, some of these effects may be of clinical benefit or lead to the production of other therapeutic agents.

With the deployment and travel of U.S. military troops into areas of high incidence of parasitic disease, the U.S. Army is certainly concerned with obtaining drug agents which work effectively and safely in preventing or curing these diseases. However, it is also obvious to us that the Army senses a responsibility to develop drugs which would not be economically feasible for commercial concerns for the treatment of such devastating world-wide diseases. The incidence and continuum of drug refractory strains among the parasite throughout the world has possibly made this task eternal.

HYPOTHESIS

Studies which are directed only or largely towards antiparasitic activity may not reveal many toxic effects or other possible therapeutic effects. We believe that many of the candidate antiparasitic drugs have other important pulmonary and cardiovascular actions which should be investigated and evaluated; this protocol describes sound methods of accomplishing this task.

EXPERIMENTAL APPROACH

The type of investigation to be conducted on a particular compound depends on its chemical structure, physical properties and the effects which it produces in preliminary experiments. The solubility of a new compound in various solvents (such as water, saline, propylene glycol or Tween 80) acceptable for introduction into test animals will have to be determined. This information will dictate the concentration of the drug preparation and the mode and duration of drug administration. The design of a study for a particular drug will be dependent on the needs of the U. S. Army Medical Research and Development Command. We anticipate that a representative of the Research and Development Command will indicate the type of administration and the types of information which are necessary or important in developing an overall understanding of the drug's potential.

PULMONARY AND CARDIOVASCULAR EFFECTS OF WR-142,490 (MEFLOQUINE)

PROTOCOL

BACKGROUND

Mefloquine, α-(2-piperidyl)-2,8 bis (trifluoromethyl-4- Quinolinemethanol HCl or WR-142,490, is an antimalarial of dramatic single-dose curing potential. Extensive oral toxicity investigations in dogs and rodents have indicated certain dose regimens create lesions in the lymphoid tissue and liver (Lee et al, 1972, 1973, 1974). Moreover, acute intravenous administration in dogs has revealed acute cardio-respiratory involvement, hemoglobinuria and massive pulmonary edema in toxic and lethal doses (63-141 mg/kg), (Lee et al., 1975). This pulmonary edema has also been noted by Minor (WRAIR, personal communication) after 70 mg/kg when mefloquine was given as a rapid i.v. infusion of 10 mg/kg/min. Accumulation of this drug in the lung has also been indicated by the appearance of radio-label in the lungs of rodents following acute and subacute oral administration the radio-labelled WR-142,490 (Bionetic labs and Rozman, 1972).

PURPOSE OF STUDY

Human usage will probably involve the intravenous administration of mefloquine necessitating information on the possible cardiovascular and pulmonary consequences of such a procedure. This proposed study will determine the effect of acute intravenous infusion of WR-142,490 in dogs on cardiovascular and pulmonary function.

OBJECTIVES

1. To determine the effects and time course of acute intravenous administration of mefloquine HCl on certain cardiovascular parameters such as: arterial blood pressure, central venous blood pressure, ascending aortic blood flow, cardiac contractile force, pulmonary artery and wedge pressure, left atrial pressure, EKG and heart rate. Additionally, limb lead EKG, atrial and ventricular electrogram and HIS bundle recording will be obtained.

2. To determine how acute intravenous administration of mefloquine affects respiratory rate, blood pH, pCO_2, pO_2, tidal volume, respiratory flow rate, intrapleural pressure, pulmonary resistance, pulmonary compliance.

3. To determine the interaction of certain modulators of pulmonary airway resistance (e.g. histamine [a bronchodilator]) with mefloquine.

EXPERIMENTAL PROCEDURES

A. Drug and Dosing

The mefloquine will be provided by Walter Reed Army Institute of Research as both the HCl and methane sulfonate salts. Because it now appears that the mefloquine HCl will be the form given to humans, this is the form which will be used in the outlined studies. However, a dog prepared for each experimental procedure listed below will be given mefloquine methanesulfonate to determine if there is any difference in the characteristics or degree of activity. Ethanol will be used initially to dissolve the WR-142,490 to a concentration of 30 mg/ml. This solution will then be diluted with 5% dextrose-water to yield a mefloquine concentration of approximately 10 mg/ml and 30% ethanol for infusion. Additional test drugs will be obtained from commercial sources and given intravenously. Appropriate controls for the vehicle will be done in each group.

B. Animals

The animals used in the proposed study will be mongrel dogs which have been conditioned by the university vivarium. This procedure includes innoculating the dog against a variety of canine diseases and ridding it of parasitic infestations. It is intended that a (50/50) mixture of the sexes can be obtained and that the weights of these animals are close to 10 kg.

C. Experiments

1. Initial studies

Preliminary experiments (see attached summary report) in our laboratory have indicated that mefloquine, at a dose rate of 10 mg/kg/min, kills dogs with no respiratory support after a cumulative dose of from 65 to 80 mg/kg. This death appears to be due to respiratory arrest. Infusion of 100 mg/kg at a dose rate of 2 mg/kg causes considerable cardiovascular despression but not death. Ideally, we would like to determine dose rate deliveries of mefloquine which 1) create no noticable cardiovascular or pulmonary effects, 2) produce obvious changes in pulmonary and cardiovascular function, and 3) produce death. Since it is now thought that humans will receive mefloquine infusion for a several hour period, we wish to mimic this time course in dogs.

We propose initially to determine what effect mefloquine has on the blood pressure, heart rate, and rate and depth of respiration of anesthetized dogs when given over a 2 hour period at rates of 0.5, 1.0 and 2 mg/kg (2 dogs at each dose rate).

From these experiments we will select a dose rate which produces obvious but not lethal changes in the parameters measured. This dose rate will then be utilized in following studies.

2. Cardiovascular Studies

Eight dogs will be anesthetized with Na pentobarbital, 30 mg/kg, i.v. and supplemented by i.m. injection of 1.5 mg/kg every 30 minutes. A femoral artery and vein will be cannulated for measurement of arterial blood pressure and the introduction of drug solutions, respectively. Another catheter will be in-

serted through the other femoral vein and will be cannulated for the measurement of central venous pressure. The chest will be opened by a sternum-splitting procedure (dog then placed on positive-pressure ventilation), the heart exposed and a Walton-Brodie strain gauge arch sewn on the right ventricle for the measurement of cardiac contractile force. The ascending aorta will be cleared of fat pads and a Carolina electromagnetic flow probe placed around it for the measurement of ascending aortic blood flow (cardiac output minus coronary blood flow). A catheter will be introduced into the left atria via a metal trochar through the atrial wall. This will be secured by a purse string suture. Pulmonary artery or pulmonary wedge pressure will be measured following placement of a Swan-Ganz catheter into the pulmonary artery or wedging it up into a smaller arterial branch. EKG and heart rate will also be monitored. Simultaneous recordings of atrial and ventricular electrograms will clearly identify any interference with A-V transmission. This will be accomplished by placement of a hexapolar electromonitoring catheter (Damato type, Electrocath Co.) in the right atrium and right ventrical (lying through the tricuspid valve commissure) following insertion through the jugular vein. These parameters will be monitored before, during and for 2 hours after the infusion of mefloquine. (See Table 1)

In these studies, the effects of certain cardiovascular agonists will be observed. The responses of certain vasoactive agents such as epinephrine, isoproterenol, histamine, acetylcholine, and serotonin will be monitored before and after the infusion of mefloquine to determine if this experimental agent potentiates or inhibits the action of these test substances. Also to be observed before and after mefloquine infusion will be the response to clamping of the carotid arteries proximal to the carotid sinus (1 minute) to determine the integrity of the carotid sinus baroreceptor pressure reflex.

3, Pulmonary function studies

The pulmonary function studies will involve eight dogs anesthetized with morphine sulfate, 2 mg/kg, s.c., followed in 30 minutes by pentobarbital sodium, 30 mg/kg, i.v. The morphine has been shown to promote a smooth level of anesthesia in respiratory function experiments. The femoral artery will be cannulated for measurement of aortic blood pressure and the femoral vein cannulated for the intravenous injection of drugs.

A catheter will be inserted into the left fifth intercostal space for measurement of intra pleural pressure. An endotracheal tube will be connected directly to a mesh screen Fleisch pneumotachograph and the pressure difference across the screen will be measured by a differential pressure transducer (Sanborn 270 or Statham PM5TC (0.15-350). The signal from the transducer corresponds to air flow and will be in turn integrated and recorded as tidal volume. Both flow and volume will be recorded. The pressure difference between the trachea and intrapleural space will be measured by a second differential transducer (Statham PM5TC 0.3-350) and also recorded. Respiratory rate will also be monitored.

The measurement of pulmonary compliance and resistance may be accomplished by two methods. One is described by Mead and Whittenberger (1953) and by Comroe et al. (1959). In principle, to measure pulmonary resistance, the flow rate (V = LPS) and pressure (P = cm H_2O) signals will be displayed simultaneously on both axes of a dual beam Tektronix oscilloscope screen to show a P-V loop. Subsequently, an amount of pressure proportional to volume will be subtracted so that the loop will be closed at zero flow. The slope of the line thus obtained

corresponds to pulmonary resistance (Δcm H_2)/LPS). The values for compliance will be obtained similarly by displaying the Pressure - Volume signals and subtracting pressure when closing the resistance loop. Pulmonary compliance is a function of the relationship between pulmonary volume and pressure (Δml/Δcm H_2O). The other method is described by Giles et al. (1971). Using the same parameters monitored above, an analog on-line computer allows breath by breath analysis of pulmonary resistance and compliance. This pulmonary mechanics computer (recently purchased from Buxco Electronics, Inc.) greatly facilitates accurate measurement and gives these values continuously (every breath) throughout the experimental period. Also monitored continuously will be respiratory rate and tidal flow and volume. To determine whether or not mefloquine affects the reactivity of bronchiolar smooth muscle, small test doses of either histamine, (a bronchoconstrictor), (5 µg/kg) or isoproterenol, (a bronchodilator), (1 µg/kg) will be given i.v. before and at various time intervals during and after administration of mefloquine.

Optional

If blood gas analyzer equipment is available, we will make repeated determination of blood pH, pO_2, and pCO_2 before, during and after infusion of mefloquine. The known pulmonary effects of high doses of mefloquine will undoubtedly cause significant changes in these parameters. It will be important to establish the extent of such changes at dose levels which approximate those projected for human use.

Robert W. Caldwell

Robert W. Caldwell, Ph.D.

Clinton B. Nash

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Table 1

Parameter/unit	Purpose	Procedure
Arterial blood pressure (mmHg)	to determine effect of drug on arterial vascular tone or cardiac function	fluid filled catheter in abdominal aorta connected to pressure transducer
Central venous pressure (mmHg)	to determine effect on venous vascular tone or ability of heart to pump blood out	fluid filled catheter in vena cava at level of heart connected to a pressure transducer
Ascending aortic blood flow (l/min)	measure of the heart's ability to pump blood; cardiac output - coronary blood flow	placement of an electromagnetic flow probe around a cleaned segment of the ascending aorta
Cardiac contractile force (gms-tension)	measure of force with which the ventricular mycardium contracts	application of a Walton-Brodie strain gauge arch to the surface of right ventricle and monitoring of transduced signal
Pulmonary artery pressure (mmHg)	to determine what effect drug has on resistance through pulmonary vascular tree or if output function of left heart is sufficient to keep up with blood flow coming to it. (Pulmonary artery diastolic pressure approximates pulmonary capillary pressure)	insertion of fluid filled catheter with balloon tip (Swan-Ganz) down jugular vein through right heart into pulmonary artery (with deflation of balloon when in artery). This catheter is attached to pressure transducer
Pulmonary wedge pressure (mmHg)	to determine pressure in pulmonary capillaries. Is there sufficient hydrostatic pressure to produce pulmonary edema?	insertion of Swan-Ganz catheter as above (5) with the advancement (wedging) of catheter tip into an arteriole or small artery. Inflation of balloon to occlude flow around catheter so only pressure in capillaries may be measured.
Left atrial pressure (mmHg)	reflects how well blood is being pumped by left ventricle; reflects pulmonary venous tone	insertion of fluid filled catheter through wall of left atrial appendage securing it by a purse-string suture

Parameter/unit	Purpose	Procedure
Pulmonary circulation time (sec)	indicates how rapid blood flows through the pulmonary vasculature. Time depends on cardiac output and volume (capitance of pulmonary vasculature)	injection of indicator dye (cardio-green) into base of pulmonary artery and collection and monitoring of small amount of pulmonary vein blood. Monitoring of dye in collected samples by use of a spectrophotometer; indicates appearance of dye in pulmonary vein blood and yields transient time.
Diffusion capacity	Provides an index of surface area in lung for gas diffusion, also an index of the dimensions of the pulmonary capillary bed and pulmonary membrane and of the efficiency of this system in the exchange of respiratory gases. Ml of a gas STPD *diffusing across the pulmonary membrane per min.* per mmHg of partial pressure difference between the alveolar air and	carbon monoxide is ideally suited for measurement because if alveolar is kept below several per cent of an atmosphere, the capacity of the hemoglobin in the blood is great enough to bind all the CO that crosses the pulmonary membrance. pCO assumed *equal to zero.* CO detected by infrared CO meter or gas chromatograph.
Blood gas and pH pH units pCO_2 pO_2 (mmHg)	measure of how well gases are being exchanged across lung; indication of availability of O_2 at level of peripheral tissue; indication of direct effect of drug on acid-base balance of blood	collect blood in heparinized syringe; cap and run in Corning blood gas analyzer (now on hand)

Parameter/unit	Purpose	Procedure
Pulmonary compliance (dynamic) ml / cm H_2O	Measure of the stretch of the pulmonary system; how pressure change occurs in airways with given changes in volume of the air system. Any intervention (drug?) which causes stiffening of airways components will decrease compliance.	Using intrapleural pressure signal and maximum tidal volume (when tidal flow is zero) determine compliance value with Buxco Pulmonary Mechanics Computer (see attached sheet)
Pulmonary resistance (dynamic) CMH_2O/LPS (liters per sec)	A measure of pressure divided by flow; a measure of the ease or difficulty encountered in the movement of air through the pulmonary airways - smaller cross-sectioned airway area creates an increase in pulmonary resistance.	using intrapleural pressure signal and maximum tidal flow signal, determine pulmonary resistance value with Buxco Pulmonary Mechanics Computer. (see attached sheet)

TABLE OF CONTENTS

Pulmonary and Cardiovascular Effects of Mefloquine Methanesulfonate

A. INTRODUCTION

Background

Mefloquine methanesulfonate, or d,l erythro α-(2-piperidyl)-2,8 bis (trifluoromethyl)-4-quinolinemethanol methanesulfonate, is an antimalarial of dramatic single-dose curing potential. Extensive oral toxicity investigations in dogs and rodents have indicated certain dose regimens create lesions in the lymphoid tissue and liver (Lee et al., 1972, 1973, 1974). Moreover, acute intravenous administration in dogs has revealed acute cardio-respiratory involvement, hemoglobinuria and massive pulmonary edema in toxic and lethal doses (63-141 mg/kg), (Lee et al., 1975). This pulmonary edema and cessation of breathing has also been noted by Minor (WRAIR, personal communication, 1975) after about a total dose of 70 mg/kg when mefloquine was given as a rapid i.v. infusion of 10 mg/kg/min. This drug has also been shown to be present in the lungs of rodents following oral administration of radio-labelled mefloquine (Rozman, WRAIR, personal communication, 1972). An earlier report on the cardiovascular effects of mefloquine HCl (Caldwell, 1972) indicated a decrease in arterial blood pressure, total peripheral vascular resistance and an increase in ascending aortic blood flow, cardiac contractile force and heart rate in dogs when mefloquine HCl was given i.v. in doses from 5 to 40 mg/kg over a period of 2 minutes. A tachyphylaxis was observed to the augmentation of aortic blood flow, cardiac contractile force and heart rate to mefloquine HCl. These stimulant effects along with the tachyphalaxis may be explained by catecholamine release since the stimulant effects were completely eliminated by previous treatment of the dogs with propranolol. During recent respiratory function experiments in this laboratory some cardiovascular responses to mefloquine MS have been observed which do not correspond to those previously reported for mefloquine HCl.

Purpose of Study

Previous animal work has demonstrated that mefloquine affects the pulmonary and cardiovascular systems. Additionally, because mefloquine methanesulfoante may be administered by the intravenous route, this study was designed to elucidate the effects of acute intravenous infusion of mefloquine methanesulfonate in dogs on pulmonary and cardiovascular function. Specifically, the objectives of this study were to determine how acute intravenous infusion of mefloquine MS affected: 1) parameters associated with respiration - respiratory rate, tidal volume, minute volume, dynamic airways compliance and dynamic airways resistance; 2) arterial and venous blood, pCO_2, pO_2 and pH and; 3) the cardiovascular parameters - arterial blood pressure, central venous pressure, pulmonary artery and wedge pressure, heart rate, ascending aortic blood flow and cardiac contractile force. Additionally, because of an observed increase in pulmonary artery pressure and pulmonary wedge pressure in acutely prepared dogs given the highest dose-rate of mefloquine MS used (3 mg/kg/min), we have attempted to determine how long these elevations persist by monitoring pulmonary artery and pulmonary wedge pressure one and four days after drug administration.

B. MATERIALS AND METHODS

Drug - preparation

Mefloquine methanesulfonate (bottle #BE 19191, Lot AL) was dissolved in deionized water for i.v. delivery. A saturated stock solution was prepared. It was determined spectrophotometrically by reading at 283 nm that 7.2 mg/ml of mefloquine MS was dissolved in our deionized water at room temperature. It is this concentration that was infused during our experiments. There is no evidence in other experiments in our laboratory or adjacent laboratories that there are any pyrogens in our water.

Animals

The animals used in this study were mongrel dogs which were obtained through the University of Tennessee vivarium. These dogs were of either sex and ranged in weight from 10 to 13 kg. These dogs were screened so that only healthy ones free of obvious disease were used in this study.

Experiments

All dogs used in these experiments were anesthetized with pentobarbital sodium, 30 mg/kg i.v. A stable level of anesthesia was maintained throughout the experiment with supplemental doses of pentobarbital sodium, 1.5 mg/kg subcutaneously every 20 minutes starting one hour after the initial dose. A femoral artery and vein were cannulated and the catheters were advanced to the level of the abdominal aorta and inferior vena cava for the measurement of arterial blood pressure and the introduction of drug solutions, respectively. Rectal temperature was continuously monitored in all dogs. The temperature of the dog was maintained between 37 and 38° C by a heating pad and lamp.

Groups of Animals: There were two main groups of dogs used in these experiments: closed-chest dogs and dogs whose chest had been opened. The following divisions indicate the number of dogs used in each group and the parameters measured in those dogs:

a. Closed-chest dogs (Group I)

Group I - Dogs which were used to measure respiratory rate, tidal volume, minute volume, airways resistance and compliance, arterial blood pressure and heart rate.

i.v. infusion for 20 minutes	Number
water control	7
1 mg/kg/min mefloquine MS	3
2 mg/kg/min mefloquine MS	4
3 mg/kg/min mefloquine MS	8

Group 1A - Those dogs in group I which were used additionally to measure pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP) and hematocrit.

i.v. infusion for 20 minutes	Number
water control	3 (2 for PAP, PWP)
1 mg/kg/min mefloquine MS	3
2 mg/kg/min mefloquine MS	4
3 mg/kg/min mefloquine MS	6 (5 for PAP, PWP)

Group 1B - Those dogs in group I which were additionally used to monitor arterial and venous blood pO_2, pCO_2, and pH.

i.v. infusion for 20 minutes	Number
water control	4
3 mg/kg/min mefloquine MS	4

Group 1C - Dogs used only to measure pulmonary artery pressure, pulmonary wedge pressure and blood volume on a subacute basis. These dogs were monitored on the day of the infusion of water or mefloquine MS, on the following day, and 4 days later.

i.v. infusion for 20 minutes	Number
water control	2
3 mg/kg/min mefloquine MS	2

b. Open-chest dogs (Group II)

Dogs which were used to measure central venous pressure, arterial blood pressure, heart rate, ascending aortic blood flow and myocardial contractile force.

i.v. infusion for 20 minutes	Number
1 mg/kg/min mefloquine MS	5
3 mg/kg/min mefloquine MS	5

Pulmonary Function: For the measurement of pulmonary function, an endotracheal tube with a side arm was connected directly to a mesh screen Fleisch pneumotachograph and the pressure difference across the screen was measured by a differential pressure transducer (Statham PM5TC 0.15-350). This signal when calibrated corresponded to tidal airflow and in turn when integrated was also recorded as tidal volume. Also, the tip of a spear-shaped catheter was inserted through the left fifth intercostal space into the pleural cavity and the shaft secured to the skin with an airtight suture for the measurement of intrapleural pressure.

The pressure difference between the trachea and intrapleural space, or transpulmonary pressure, was measured by a second differential pressure transducer (Statham PM5TC 0.3-350).

Respiratory dynamic airways resistance and dynamic airways compliance were computed by introduction of the above electrical signals into a Buxco Electronics Pulmonary Mechanics Computer. This on-line analog computer performed necessary calculations after each breath and gave resistance and compliance signals which were displayed on a Grass polygraph. The basic method was described by Giles et al., (1971). Previous calibration of this computer with known flow and pressure signals provided a calibration standard for tidal volume, resistance and compliance.

To determine whether or not mefloquine MS affected the reactivity of bronchiolar smooth muscle, small test doses of either histamine (a bronchoconstrictor), 5 μg/kg, or isoproterenol (a bronchodilator), 1 μg/kg, were given i.v. before and just after infusion of the candidate antimalarial.

Blood gases - For the measurement of blood pO_2, pCO_2, and pH, catheters were placed in the left ventricle or in the aortic arch to obtain arterial blood and placed in the right atrium or the pulmonary artery to obtain venous blood. Blood gases and pH were determined on an Instrumentation Laboratory Model 213 Blood Analyzer. Blood samples taken in syringes were capped and kept on ice from the sampling time until they were analyzed. In no case was this time period longer than 30 minutes.

Cardiovascular Function - closed-chest dogs - Systolic, diastolic, and pulse pressure were measured by an indwelling aortic catheter attached to a Statham pressure transducer. Heart rate was recorded by a Grass cardiotachometer which was triggered by the R wave of a Lead II EKG.

A Swan-Ganz catheter was used to measure pulmonary artery and pulmonary wedge pressure (Swan et al., 1970). The Swan-Ganz catheter with balloon partially inflated was advanced through the right jugular vein, the right heart and into the pulmonary artery until a pressure resembling pulmonary artery wedge pressure was obtained. The balloon was then deflated and the catheter advanced 1 to 3 cm. Upon reinflation of the balloon on the tip of this catheter, pulmonary wedge pressure, which is an assessment of left atrial pressure, was obtained. Balloon inflation for wedge pressure measurement was not performed more frequently than every 10 minutes and lasted for only 5-10 seconds to preclude possible pulmonary infarction. Verification of correct placement was made after the sacrifice of the dog.

Central venous hematocrits were measured throughout the observation period by the microcapillary method.

Subacute Studies:

An additional small group of 4 dogs (Group IC) was used in a 5 day subacute study. The dogs were anesthetized and prepared as described above to measure pulmonary artery pressure, pulmonary wedge pressure, aortic blood pressure, EKG, plasma volume and blood volume. On their first day, these dogs were given either 3 mg/kg/min of mefloquine MS (2) or a comparable volume of water (2) and monitored for 3 hours. At the end of this observation period the cannulae were removed and the vessels ligated as far distally from the heart as possible. The dogs were treated with 1 cc of flocillin, subcutaneously and returned to a recovery cage.

On the first day and the fifth day following drug dosing, the animals were again prepared as described above. Following a 45 minute equilibration period after surgery, the dogs were again monitored every 15 minutes for an hour for the parameters previously described. Following the last observation period, the dogs were sacrificed.

The plasma volume of these dogs was estimated by the dye dilution method modified (Guyton, 1976) after the original description by Keith et al (1915). The blood volume was obtained by adding the plasma volume to a corrected cell volume. A known amount of dye, T-1824 or Evans Blue, was injected into the dogs and blood samples taken 10, 20 and 30 minutes later. This procedure was performed before and 3 hours after treatment on the first day and again during the observation period on the following and fifth day.

Cardiovascular Function, open-chest dogs: In 10 dogs, the chest was opened by a sternum-splitting procedure and the dog was then placed on a Harvard respirator. The heart was then exposed and a Walton-Brodie strain gauge arch was sewn on the right ventricle for the measurement of cardiac contractile force. The movable feet of this gauge were stretched apart to the point where a maximum tension excursion was noted and the length of the gauge was fixed. This is the plateau of the Frank-Starling curve. This gives contractile force changes which are minimumly affected by changes in venous return. Additionally, the ascending aorta was cleared of fat pads and a Carolina electromagnetic flow probe placed around it for the measurement of ascending aortic blood flow (cardiac output minus coronary blood flow). Lead II EKG, arterial blood pressure and heart rate were also monitored. In open-chest dogs, an additional fluid filled catheter was advanced from a femoral vein to the level of the right atrium for measurement of central venous pressure.

In 3 of the open-chest dogs, the cardiovascular responses to i.v. norepinephrine (0.5 mg/kg), isoproterenol (0.25 mg/kg) and acetylcholine (2 mg/kg) were observed before and 20 minutes after the infusion of 3 mg/kg/min of mefloquine MS or a total dose of 60 mg/kg.

Drug Delivery: Mefloquine MS was given at dose-rates of 1, 2, or 3 mg/kg/min for 20 minutes or cumulative total doses of 20, 40 and 60 mg/kg. The drug was always dissolved in deionized water. The volume-rate of drug solution infused for 20 minutes varied from 2 to 7.6 ml/min depending on the dose-rate and weight of the dog. A water infusion control was also included at the rate of 5 ml/min for 20 minutes in 7 dogs.

Data: Our data are presented as mean absolute values ± the standard error of the mean (S.E.M.) if control period value variability between animals of a particular drug dose group was not large. If the variability of control values for a dose groups was large, mean percent change ± S.E.M. from a 30 minute control period was plotted. The percent change reference level was the average of 4 points during the 30 minute control period for a particular drug dose group (-30, -20, -10, and 0 minutes). For an estimate of variability during this period, the difference between this 4 point mean and the mean for the -10 minute period is given. The number of dogs used for each data point is given in the legend for each figure.

C. RESULTS

Pulmonary Function:

Respiratory rate changes were not markedly different between the 1 mg/kg/min mefloquine MS group and the water infusion control (Table 1). Although the beginning respiratory rate of the 1 mg/kg/min group was higher than the water control, both groups demonstrated a slow progressive rise in rate during the observation period. The dose-rates of 2 and 3 mg/kg/min of mefloquine MS did produce higher respiratory rates during and just after the drug infusion but respiratory rate tended to return to pre-drug values during the remainder of the observation period.

Figure 1 indicates the changes in respiratory tidal volume with infusion of H_2O or 1, 2 or 3 mg/kg/min of mefloquine MS for 20 minutes. Control tidal volume values ranged from 250 ml to 600 ml. Mefloquine MS, in the 2 and 3 mg/kg/min dose-rates, caused similar decreases in tidal volume during the drug infusion with a return to control values within 40 minutes following drug infusion. The 1 mg/kg/min dose-rates did not appear to affect tidal volume during the infusion, but tidal volume tended to fall in this group as the observation period progressed.

Minute volume, which is the product of average tidal volume times number of respirations per minute, changed differently with the infusion of mefloquine MS than did tidal volume (Fig. 2). It appeared that all tested doses of mefloquine MS increased minute volume during the drug infusion over the water infusion control values, but there was no apparent dose-rate relationship. After the drug infusion, the minute volume of the 1 mg/kg/min group tended to remain elevated while values in the two other dose-rate groups diminished.

Dynamic pulmonary compliance did not appear to be affected during the infusion of mefloquine MS (Fig. 3). There was a tendency for compliance values to fall in all groups of dogs during the 210 minute observation. It should be noted that compliance values late in the observation period were lowest in the dogs receiving 1 mg/kg/min.

Dynamic pulmonary airways resistance was decreased in a dose-rate related manner during the infusion of 1, 2 and 3 mg/kg/min of mefloquine MS (Fig. 4). However, both the 2 and 3 mg/kg/min groups exhibited gradually rising resistance values starting about 10 minutes after the cessation of drug administration. These values continued to rise the remainder of the observation period. The resistance values for the 1 mg/kg/min group were not different from those of the water control except late in the observation period. At this time they were elevated.

A small test dose of histamine, 5 μg/kg i.v., produced approximately a 30 to 35 percent increase in airways resistance both before and just after the infusion of 1, 2 or 3 mg/kg/min of mefloquine MS. Likewise, the test dose of isoproterenol, 1 μg/kg i.v., produced approximately a 20 percent decrease in airways resistance both before and just after the infusion of all tested doses of mefloquine MS. Therefore, mefloquine did not appear to block the action of these two broncho-active agents.

A representative tracing of pulmonary signals is given in Figure 5. This figure indicates portions of the polygraph recordings for tidal volume, compliance and resistance at various times before, during, and after the infusion of mefloquine MS at a dose of 3 mg/kg/min. Each pen excursion indicates a breath.

Figure 6 indicates the effects of mefloquine MS or water infusion upon arterial blood pO_2 and pCO_2. Arterial blood pO_2 values for the mefloquine MS and water group were not different during the experimental period although there was a tendency for pO_2 to rise in both groups with solution infusion. The arterial blood pCO_2 values also were not different between the two groups, with both groups of animals exhibiting stable values throughout the observation period. Arterial blood pH values were not different between the mefloquine MS and water infused groups (pH range among various dogs, 7.31 to 7.45).

Figure 7 indicates the effects of mefloquine MS or water infusion upon venous blood pCO_2 and pO_2. Mefloquine MS caused no change in venous blood pCO_2 during the infusion but the pCO_2 of this treated group progressively increased over the water control through the remainder of the observation period. Conversely, the venous blood pO_2 of the drug treated group, while not differing from the water control during the infusion sequence, fell below the water infused group during the remainder of the observation period. Venous blood pH was not different between the mefloquine MS and water infused groups (pH range among various dogs, 7.26-7.35)

<u>Cardiovascular Function - closed-chest:</u> Diastolic blood pressure values during and following infusion of mefloquine MS, 1 mg/kg/min, were not appreciably different from those of the water control (Fig. 8). However, a marked and dose related drop in diastolic pressure was noted for the 2 and 3 mg/kg/min dose-rates during the 20 minute infusion. Within 25 minutes following the infusion the diastolic blood pressure values of these groups were not different from the water control.

Systolic blood pressure values for these groups demonstrated a similar pattern (Fig. 9). The 1 mg/kg/min dose-rate of mefloquine did not change systolic blood pressure from water control values during or following the infusion. The 2 mg/kg/min group seemed to have a slightly higher systolic pressure than the water group which persisted throughout the observation period. The 3 mg/kg/min dose-rate caused a transient depression in systolic blood pressure values, which returned to control values soon after the cessation of the mefloquine infusion.

Pulse pressure appeared to increase during the infusion of 1 mg/kg/min of mefloquine and return to control values thereafter (Fig. 10). The pulse pressure for the 2 mg/kg/min group tended to rise during the infusion and fell to control levels about 40 minutes after the infusion. The 3 mg/kg/min dose-rate of mefloquine did not appear to appreciably alter pulse pressure during or following the infusion.

Pulmonary wedge pressure, an estimate of left atrial pressure, rose during and after infusion of mefloquine MS (Fig. 11). There was no clear dose-rate relationship to this gradual increase. Indeed, values in the 2 mg/kg/min group tended to fall later in the observation period. The dogs infused with water showed no change in pulmonary wedge pressure throughout the observation period. Pulmonary artery pressure, which was also monitored in these dogs, rose during 2 and 3 mg/kg/min infusion (Fig. 12). The values for the 3 mg/kg/min dose-rate group were still

elevated at the end of the observation period, but the values for the 2 mg/kg/min returned toward the pre-drug control level by the end of the observation period. Like the wedge pressure, there was no clear dose-rate relationship to this observed elevation. The 1 mg/kg/min dose-rate caused no initial effect on pulmonary artery pressure, but the group demonstrated elevated values at the end of the observation period.

Heart rate decreased during the infusion of 2 and 3 mg/kg/min of mefloquine MS (Fig. 13) and remained low throughout the observation period. Throughout the observation period, the water control and 1 mg/kg/min groups demonstrated essentially the same heart rate.

Although hematocrit values seemed stable in all groups, a trend toward increasing hematocrit values following the infusion of mefloquine MS or H_2O was observed (Table 22). This trend peaked at about +75 minutes after the infusion and then returned to near control period values by +180. Inspection of the capillary tubes following spinning revealed a red color in the plasma of all dogs which had received 2 or 3 mg/kg/min of mefloquine MS. This red color, which may be indicative of hemolysis, was apparent by the end of the infusion period. Of the 3 dogs which received 1 mg/kg/min of mefloquine MS, one had red plasma after the end of the infusion. None of the 3 dogs receiving water had any evidence of hemolysis.

<u>Subacute Study</u>:

Three of the 4 dogs, whether given water or mefloquine, reacted acutely very similarly to dogs previously studied which received the same treatment. However, one dog reacted quite differently. Dog #1, the first dog of this series to receive mefloquine MS, 3 mg/kg/min, had a dramatic drop in aortic blood pressure of 65% during the drug infusion (from a mean of 110 down to 38 mmHg). This degree of hypotension was by far the most marked observed in any dog given 3 mg/kg/min of mefloquine MS for 20 minutes. This dog, which appeared quite active before the study, did not recover from the anesthesia as rapidly as the other dogs studied and appeared quite listless before administration of the anesthetic on the second day. On the fourth day following drug administration, this dog died. A post mortem examination by the University veterinary pathologist, Dr. Jack R. Hessler, revealed a very marked pulmonary edema with some evidence of leukocyte infiltration in the lung and considerable vascular congestion in the kidneys.

The subacute effects of infusion of either water or mefloquine MS, 3 mg/kg/min upon pulmonary artery pressure, pulmonary wedge pressure and blood volume are given in figures 14, 15 and 16. Figure 14 indicates the mean pulmonary artery pressure values. Mefloquine MS produced an immediate elevation in pulmonary artery pressure in dog #1 and #3, which persisted during the initial observation period. However, on the following day pulmonary artery pressure values in these dogs were back to pre-drug control values. On the fifth day following mefloquine MS, the values for dog #3 were still down at pre-drug control levels. Dogs #2 and #4 which were treated only with water demonstrated essentially no change in their values throughout the observation periods.

Figure 15 indicates pulmonary wedge pressure values. As noted in other dogs, mefloquine MS produced a rapid elevation in these values and this elevation tended to persist throughout the initial observation period. By the following

day, as was observed with pulmonary artery pressure, the pulmonary wedge pressure values were reduced to near the pre-drug control levels. Again, on the fifth day following mefloquine MS, the values for dog #3 were still about the pre-drug control levels. Both dogs which were treated with only water had essentially unchanging pulmonary wedge pressure values during the course of observation.

Plasma and blood volume values for these dogs are given in Figure 16. Although there is a considerable variation in the plasma and blood volume values among the four dogs, there was no difference observed in the volume within a particular dog during the 5 day experimental period. Mefloquine MS at this dose does not appear to affect blood or plasma volume.

Cardiovascular Function - open chest dogs: The effects of 1 and 3 mg/kg/min of mefloquine MS on cardiac contractile force (CF) are shown in the first panel of Figure 17. In the 1 mg/kg/min group, cardiac contractile force varied little from the control period level until late in the observation period. By +100 minutes contractile force diminished by 16% and remained at this level. During infusion of the 3 mg/kg/min dose, contractile force fell rapidly, decreasing about 20% by +5 minutes. A maximum reduction of 38% was observed at the end of the infusion. However, cardiac contractile force did recover and reached levels similar to those in the 1 mg/kg/min dose group at about +90 minutes.

The second panel of Figure 17 shows the effects of mefloquine MS on ascending aortic blood flow. Both the 1 and 3 mg/kg/min dose-rates may have slightly increased aortic blood flow initially but this effect was transient. Ascending aortic blood flow in both groups remained near pre-drug levels until about +70 minutes when it began to decline. Ascending aortic blood flow for the 3 mg/kg/min group was lower than the 1 mg/kg/min group during the last 50 minutes of the observation period.

Effects of mefloquine MS on central venous pressure are given in the lower panel of Figure 17. Although the 1 mg/kg/min and 3 mg/kg/min dose-rate groups had different initial central venous pressure values, only during the infusion of mefloquine MS 3 mg/kg/min did the central venous pressure rise above its own control level. This rise ended abruptly with cessation of mefloquine MS infusion at +20 minutes and pressure values returned to control levels by +40 minutes. The 1 mg/kg/min dose-rate did not affect central venous pressure during the observation period.

Arterial blood pressure responses to mefloquine MS in the open-chest dogs were essentially the same as those observed in similarly dosed closed-chest dogs (Table 3). Heart rate responses to mefloquine MS in these open-chest dogs were also similar to those noted in the closed-chest dogs (Table 4).

Diastolic blood pressure responses to the test doses of norepinephrine, acetylcholine and isoproterenol observed before and 20 minutes after the infusion of mefloquine MS at both the 1 and 3 mg/kg/min rate were not different. Mefloquine MS did not appear to affect the cardiovascular action of these agents.

A representative tracing of the effects of a 3 mg/kg/min infusion of mefloquine MS on ascending aortic blood flow, central venous pressure, arterial blood pressure, cardiac contractile force, lead II EKG, and heart rate is given in Figure 18. Ascending aortic blood flow remained fairly steady during the infusion, but fell gradually through the remainder of the experimental period. Central venous pressure, although beginning at a high level, went even higher during the infusion of mefloquine MS but decreased steadily following the infusion and for the remainder of the experiment. A very marked but transient drop in arterial blood pressure was observed during the infusion of mefloquine MS, 3 mg/kg/min. By +40 minutes systolic pressure had rebounded above control with an accompanying increase in pulse pressure. This effect subsided somewhat by the end of the experimental period. A prolongation of the P-R interval was noted during the infusion of this dose-rate but the P-R interval returned to control values rapidly after cessation of drug administration. Contractile force decreased during the infusion period and by +40 minutes little recovery had occurred. But by +120 minutes, values were very near that seen at time 0.

DISCUSSION

Mefloquine methanesulfonate when infused at a dose-rate of 1 mg/kg/min for 20 minutes caused little or no effect on the pulmonary and cardiovascular parameters measured, but mefloquine MS produced pronounced changes on these parameters when infused at the rate of 3 mg/kg/min for this same period of time. The magnitude of the effects of mefloquine MS appeared to be dependent on the dose-rate of drug delivery, as the effects of a given total dose were more pronounced when administered at a higher dose-rate (compare contractile force in Figure 17 - 1 mg/kg/min at 20 minutes vs 3 mg/kg/min at 7 minutes).

Certain respiratory parameters were affected more than others by mefloquine MS. Tidal volume was depressed during the infusion of mefloquine MS, but during this infusion period respiratory rate was generally increased. The net result of both of these changes was minute volume values which did not change remarkably. The initial rise in minute volume for the dogs receiving 1 mg/kg/min of mefloquine MS resulted mainly from a rise in respiratory rate during this period. To temper this observation, it must be pointed out that the respiratory rate for the 1 mg/kg/min group was higher than the other 3 groups at all time periods and may reflect some anesthesia problems in those dogs.

It is worthy of note that during the infusion period when tidal volume was depressed by mefloquine MS, an initial depression in airways resistance was also observed for the 2 and 3 mg/kg/min groups. This initial reduction in airways resistance during this shallow and rapid respiration could be related to reduced air flow through smaller bronchioles and alveoli which contribute heavily to resistance. The gradual secondary increase in airways resistance which occurred in the 2 and 3 mg/kg/min groups is presently unexplained but may be related to an accumulation of exudate in the airways.

Dynamic airways compliance, which is calculated by dividing the lung volume change during a tidal breath by the simultaneous intrapleural pressure change, was not different among the dose-rates of mefloquine MS tested and the H_2O control.

In fact, all groups demonstrated a slow depression in dynamic compliance. This gradual reduction in dynamic compliance might be due to slow fluid accumulation in the lungs of the supine anesthetized dogs. Such an accumulation of fluid may dilute the surfactant, increase surface tension and thus decrease compliance (Slonim and Hamilton, 1971).

The effect of 3 mg/kg/min, or a total dose of 60 mg/kg, of mefloquine MS on blood pO_2, pCO_2 and pH was generally not remarkable. However, several points of difference were noted between the drug and water treated groups. Arterial pO_2 for the two groups, while not being different initially, was slightly lower in the mefloquine MS group at 90 and 120 minutes after the beginning of the infusion. This reduction in arterial pO_2 could be related to the increased resistance to pulmonary airflow previously noted for this group of dogs. The short initial increase in arterial pO_2 noted in both groups during the infusion of drug or water cannot be easily explained, but may in some way be correlated with the initial depression in airway resistance. Arterial pCO_2 was remarkably stable and the same in both groups of dogs.

Both the venous blood pO_2 and pCO_2 values indicated differences between these two groups of dogs. The venous pO_2 of the water control group fell gradually. This is probably due to the gradual loss of blood volume, which actually occurs in all of the preparations, with resultant greater extraction of oxygen from the remaining blood volume. The group treated with mefloquine MS demonstrated venous pCO_2 values which rose above their own control period values and the water control group. This elevation in venous pCO_2 is probably related to a state of hypoperfusion of various organ beds. Aortic blood flow has been shown to be reduced at a time when the elevated venous pCO_2 values occurred. A reduced flow rate through an organ capillary bed could result in a higher venous pCO_2. The fall in venous pO_2 noted in the group treated with mefloquine MS supports the hypothesis that mefloquine MS is increasing extraction of O_2 from blood by the peripheral tissues.

The cardiovascular effects of mefloquine MS also varied depending on the dose-rate and the parameter measured. Arterial blood pressure decreased with both 2 and 3 mg/kg/min infusions of mefloquine MS in both open-chest and closed-chest dogs. And since ascending aortic blood flow remained the same during the majority of this hypotension, it appears that the depressor effect of mefloquine was due to a direct or indirect decrease in total peripheral vascular resistance. A slight increase in pulse pressure noted during and immediately after the 1 mg/kg/min infusion of mefloquine MS is similar to the findings of earlier experiments with mefloquine HCl (Caldwell, 1972). However, none of the present experiments with mefloquine MS show any stimulation of the myocardial contractile force as was observed for a previous lot and preparation of mefloquine HCl. Indeed, our present experiments indicate that mefloquine MS has no myocardial stimulating effects. It is possible that the increase in pulse pressure noted for the low-dose group may be a consequence of the slower heart rates observed in this group. The changes observed in the lead II EKG pattern during 3 mg/kg/min infusion, such as a depressed R and T wave, are most likely related to the hypotension produced by mefloquine MS. There is also evidence of lengthening of P-R interval during the infusion of this dose-rate of mefloquine MS. An increase in P-R interval or a reduction in A-V node conduction velocity has been noted for other quinolines and 4-aminoquinolines.

The dose-rates of 2 and 3 mg/kg/min of mefloquine MS appeared to depress cardiac function. This was reflected by a decrease in cardiac contractile force and heart rate, and also an increase in central venous pressure. Additionally, the elevation of pulmonary wedge pressure noted with the infusion of the two higher doses indicates that left atrial pressure may have been elevated. An elevation in left atrial pressure may denote some degree of left ventricular failure. The observed elevation in pulmonary artery pressure could have been related to the inability of the left heart to maintain blood flow or, alternatively, could have been due to an increase in pulmonary vascular resistance.

The subacute study demonstrated that any elevation in pulmonary artery or pulmonary wedge pressure created by the 3 mg/kg/min dose-rate of mefloquine MS was not permanent. Both dogs so treated exhibited pre-drug control values for these measurements on the day following drug administration. Since blood volume did not change appreciably in any dog during this study, any observed hemodynamic changes were unrelated to blood volume changes. The autopsy information on the mefloquine MS treated dog which died is not sufficient to allow us to determine whether the dog died as a result of drug infusion or a preexisting condition.

In summary, it appears from our group of experiments that mefloquine MS at a low dose-rate of 1 mg/kg/min causes little or no effect upon the pulmonary and cardiovascular parameters which we measured. However, dose-rates of 2 and 3 mg/kg/min of mefloquine MS for 20 minutes did produce pulmonary and cardiovascular changes. The respiratory parameters which were observed to change were: 1) tidal volume, which fell during the drug infusion but then returned to control values during the remaining portion of the observation period; 2) respiratory rate, which rose during the drug infusion but returned to control levels; 3) dynamic airways resistance, which fell during drug administration but then rose above control levels and 4) small gradual changes in blood pO_2 and pCO_2. The cardiovascular parameters observed to change were: 1) arterial blood pressure, which fell during the drug infusion but returned rapidly to control levels; 2) cardiac contractile force, which fell during the drug infusion and returned toward control levels later in the observation period; 3) central venous pressure, which rose transiently during drug administration; 4) pulmonary artery pressure, which rose initially but tended to fall late in the observation period and 5) pulmonary wedge pressure, a measure of left atrial pressure, which rose and was maintained throughout the 3 hour observation period but which returned to control levels within a 24 hour period.

TABLE 1

Effect of Mefloquine MS and H_2O Infusion
Upon Respiratory Rate (breaths/min.)

TIME (min)	(N=7) H_2O Control	MEFLOQUINE MS (N=3) 1 mg/kg/min	MEFLOQUINE MS (N=4) 2 mg/kg/min	MEFLOQUINE MS (N=8) 3 mg/kg/min
Time	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
-30	15.71 ± 3.42	26.66 ± 5.60	18.75 ± 1.43	14.56 ± 3.06
-20	16.64 ± 4.38	24.66 ± 4.48	17.25 ± 2.01	15.25 ± 3.51
-10	15.42 ± 3.92	23.33 ± 4.17	17.75 ± 2.17	15.37 ± 3.51
Infusion → 0	15.21 ± 3.72	22.66 ± 4.37	18.75 ± 1.92	15.87 ± 3.80
+10	15.42 ± 4.04	25.66 ± 6.06	21.75 ± 2.86	19.87 ± 4.74
→ +20	14.28 ± 3.98	27.00 ± 5.50	24.25 ± 3.42	22.75 ± 4.41
+30	15.92 ± 4.51	27.33 ± 2.84	23.25 ± 4.81	19.37 ± 3.48
+45	16.42 ± 4.77	32.00 ± 4.16	20.50 ± 3.96	16.87 ± 3.16
+60	18.00 ± 5.99	31.33 ± 7.96	18.50 ± 3.30	15.37 ± 2.96
+75	18.00 ± 4.83	31.66 ± 6.35	18.75 ± 2.77	15.12 ± 2.98
+90	19.00 ± 5.17	35.00 ± 6.50	19.25 ± 3.14	14.62 ± 2.96
+105	21.14 ± 5.22	37.33 ± 7.17	21.75 ± 4.24	16.00 ± 3.33
+120	20.85 ± 6.02	43.33 ± 6.33	21.75 ± 4.08	16.50 ± 3.97
+150	21.71 ± 6.55	44.00 ± 8.54	21.50 ± 4.64	19.18 ± 4.10
+180	23.85 ± 7.58	46.66 ± 10.41	22.75 ± 4.51	N=7 21.57 ± 5.82
+210	22.00 ± 8.61	44.66 ± 7.79	25.00 ± 4.63	N=7 21.85 ± 5.98

TABLE 2

Effect of Mefloquine MS and H_2O Infusion
Upon Venous Blood Hematocrit (percent)

	TIME (min)	(N=3) H_2O Control	MEFLOQUINE MS (N=3) 1 mg/kg/min	(N=3) 2 mg/kg/min	(N=6) 3 mg/kg/min
	Time	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
	-30	41.33 ± 0.84	35.16 ± 0.70	33.00 ± 1.28	N=5 38.50 ± 3.27
	-20	41.33 ± 0.84	36.00 ± 0.44	34.00 ± 0.54	N=5 36.70 ± 1.94
	-10	40.33 ± 1.20	36.83 ± 0.40	34.33 ± 0.98	N=4 35.25 ± 5.68
	0	41.66 ± 1.22	36.83 ± 0.74	35.66 ± 3.27	37.00 ± 2.10
Infusion	+10	42.66 ± 1.51	40.33 ± 0.75	39.16 ± 2.13	40.08 ± 1.51
	+20	41.66 ± 2.37	39.66 ± 0.20	37.80 ± 1.39	41.50 ± 2.86
	+30	43.00 ± 2.54	40.83 ± 1.04	40.66 ± 1.66	40.33 ± 1.72
	+45	44.50 ± 1.28	40.33 ± 1.51	39.16 ± 2.07	41.41 ± 2.15
	+60	44.83 ± 1.95	39.33 ± 1.38	37.00 ± 2.51	39.83 ± 2.21
	+75	N=2 47.50 ± 1.18	40.16 ± 0.94	39.83 ± 1.34	39.91 ± 2.21
	+90	42.66 ± 2.91	38.50 ± 1.68	39.50 ± 1.68	39.41 ± 2.04
	+105	43.16 ± 1.00	38.00 ± 1.93	39.80 ± 1.49	N=5 39.00 ± 1.84
	+120	43.83 ± 2.38	37.83 ± 1.66	39.66 ± 1.20	40.33 ± 2.01
	+150	45.66 ± 1.87	39.66 ± 1.53	35.33 ± 1.11	N=5 39.90 ± 2.97
	+180	47.00 ± 1.91	35.00 ± 1.00	34.50 ± 1.40 *	N=5 36.80 ± 1.66
	+210	45.66 ± 2.28	38.16 ± 1.16		N=5 37.70 ± 1.93

* Indicates last point where N = 3

TABLE 3

Effect of Mefloquine MS Infusion
Upon Arterial Blood Pressure (mmHg) on Open-chest Dogs

TIME (min)	(N=5) 1 mg/kg/min	(N=5) 3 mg/kg/min
Time	Mean ± SEM+	Mean ± SEM+
-30	135.00/91.40 ± 09.74/09.64	136.75/88.75 ± 08.49/07.46*
-20	112.60/73.20 ± 15.48/10.33	130.40/83.40 ± 06.21/04.24
-10	107.60/67.40 ± 15.22/10.54	130.40/41.40 ± 04.96/03.91
Infusion → 0	113.40/72.00 ± 12.48/08.08	129.00/81.20 ± 05.32/04.74
+ 5	111.40/68.20 ± 11.74/08.55	110.00/56.40 ± 12.34/08.29
+10	113.40/67.60 ± 10.10/05.06	111.40/59.00 ± 15.65/09.79
+15	115.60/68.40 ± 10.11/04.47	108.40/57.80 ± 19.82/12.44
→ +20	118.40/69.80 ± 10.53/05.53	95.60/46.20 ± 19.98/10.65
+25	126.20/77.00 ± 09.72/05.83	116.20/68.00 ± 18.72/13.85
+30	126.00/77.00 ± 11.55/07.27	140.60/75.00 ± 15.32/09.48
+40	123.00/77.60 ± 10.53/07.72	137.00/81.00 ± 10.19/07.60
+50	123.20/75.40 ± 10.26/01.00	148.40/86.60 ± 11.07/06.82
+60	129.60/73.60 ± 13.47/08.68	150.40/88.60 ± 11.45/07.67
+70	119.40/71.00 ± 11.15/07.64	146.00/88.60 ± 11.66/08.59
+80	124.00/72.00 ± 12.86/08.53	145.00/84.60 ± 11.06/09.46
+90	127.00/76.00 ± 12.86/09.13	143.00/86.00 ± 12.40/12.08
+100	123.60/74.00 ± 10.90/07.96	149.00/88.40 ± 12.88/11.76
+110	121.00/74.00 ± 09.40/06.20	142.00/84.80 ± 12.60/12/98
+120	129.60/78.00 ± 11.87/06.92	135.20/82.00 ± 13.06/13.79
+130	128.60/79.40 ± 13.61/05.18	127.40/77.60 ± 14.28/14.80
+140	124.60/76.60 ± 12.59/05.96	126.02/77.00 ± 14.01/15.70
+150	127.20/77.60 ± 10.70/05.67	113.05/64.25 ± 15.39/16.76*

* N=4

+ systolic pressure/diastolic pressure ± SEM of each of these pressures

TABLE 4

Effect of Mefloquine MS
Upon Heart Rate (beats/min.)
On Open-chest Dogs

TIME (min)	(N=5) 1 mg/kg/min	(N=5) 3 mg/kg/min
Time	Mean ± SEM	Mean ± SEM
-30	153.40 ± 3.94	174.5 ± 5.18
-20	155.00 ± 4.47	180.0 ± 4.47
-10	149.80 ± 5.95	175.2 ± 9.64
0	152.00 ± 3.74	173.8 ± 7.47
+5	149.40 ± 5.68	157.1 ± 13.77
+10	146.60 ± 4.62	145.6 ± 13.81
+15	146.20 ± 8.55	138.4 ± 13.13
+20	143.00 ± 7.78	127.4 ± 13.10
+25	144.00 ± 6.20	127.4 ± 11.42
+30	146.00 ± 4.70	127.6 ± 11.30
+40	145.20 ± 3.67	139.6 ± 10.68
+50	148.00 ± 5.83	134.0 ± 11.11
+60	149.60 ± 6.79	134.4 ± 10.06
+70	145.20 ± 6.40	135.6 ± 9.04
+80	147.00 ± 6.24	139.0 ± 9.53
+90	153.60 ± 5.74	139.2 ± 10.05
+100	148.00 ± 4.35	141.0 ± 10.29
+110	154.00 ± 5.09	137.0 ± 10.19
+120	154.00 ± 5.78	136.4 ± 6.74
+130	153.00 ± 7.00	135.4 ± 6.86
+140	148.00 ± 6.44	137.4 ± 7.95
+150	151.00 ± 5.56	137.4 ± 7.95

Infusion

TIDAL VOLUME

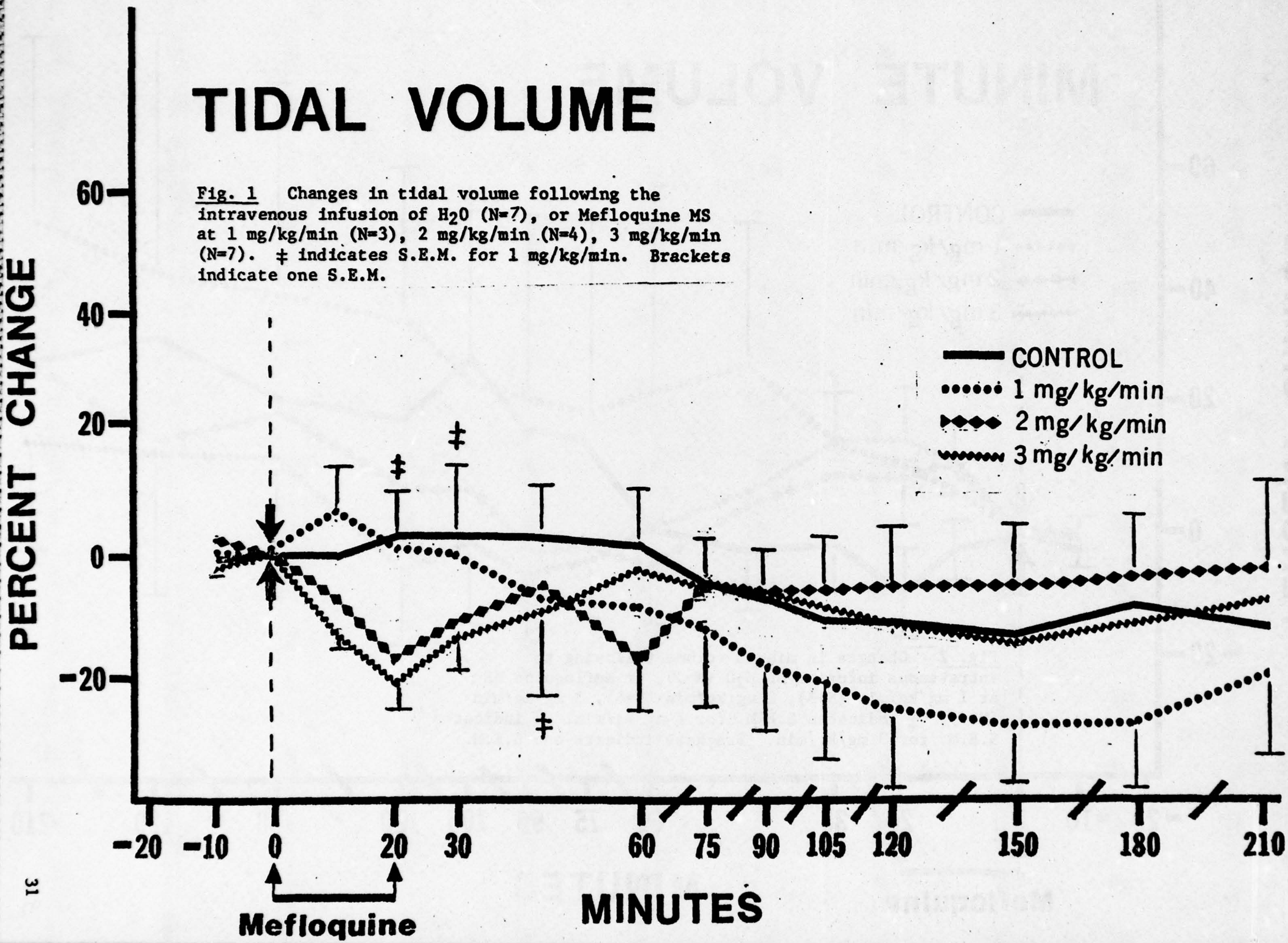


Fig. 1 Changes in tidal volume following the intravenous infusion of H_2O (N=7), or Mefloquine MS at 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), 3 mg/kg/min (N=7). ‡ indicates S.E.M. for 1 mg/kg/min. Brackets indicate one S.E.M.

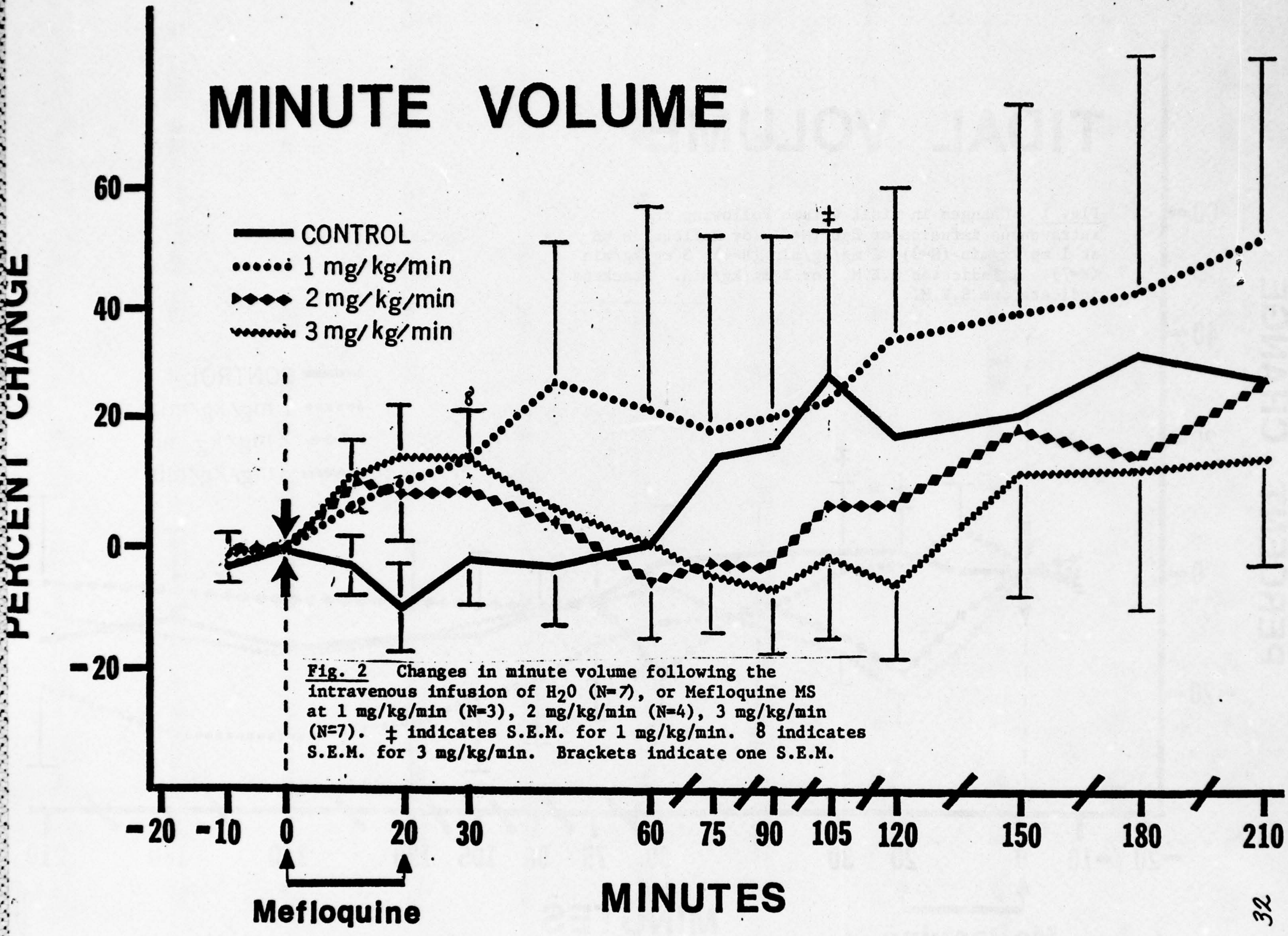


Fig. 2 Changes in minute volume following the intravenous infusion of H_2O (N=7), or Mefloquine MS at 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), 3 mg/kg/min (N=7). ‡ indicates S.E.M. for 1 mg/kg/min. 8 indicates S.E.M. for 3 mg/kg/min. Brackets indicate one S.E.M.

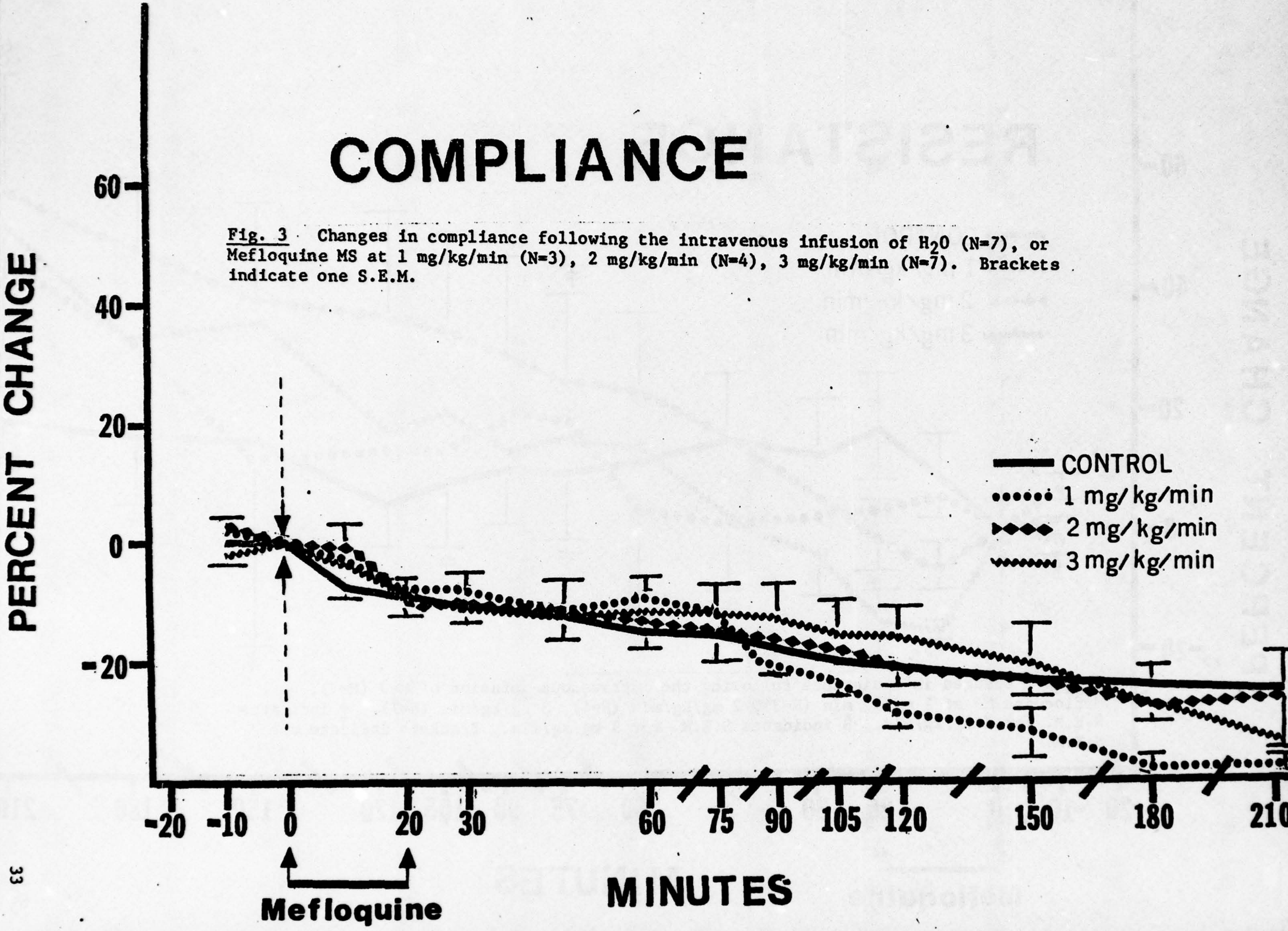
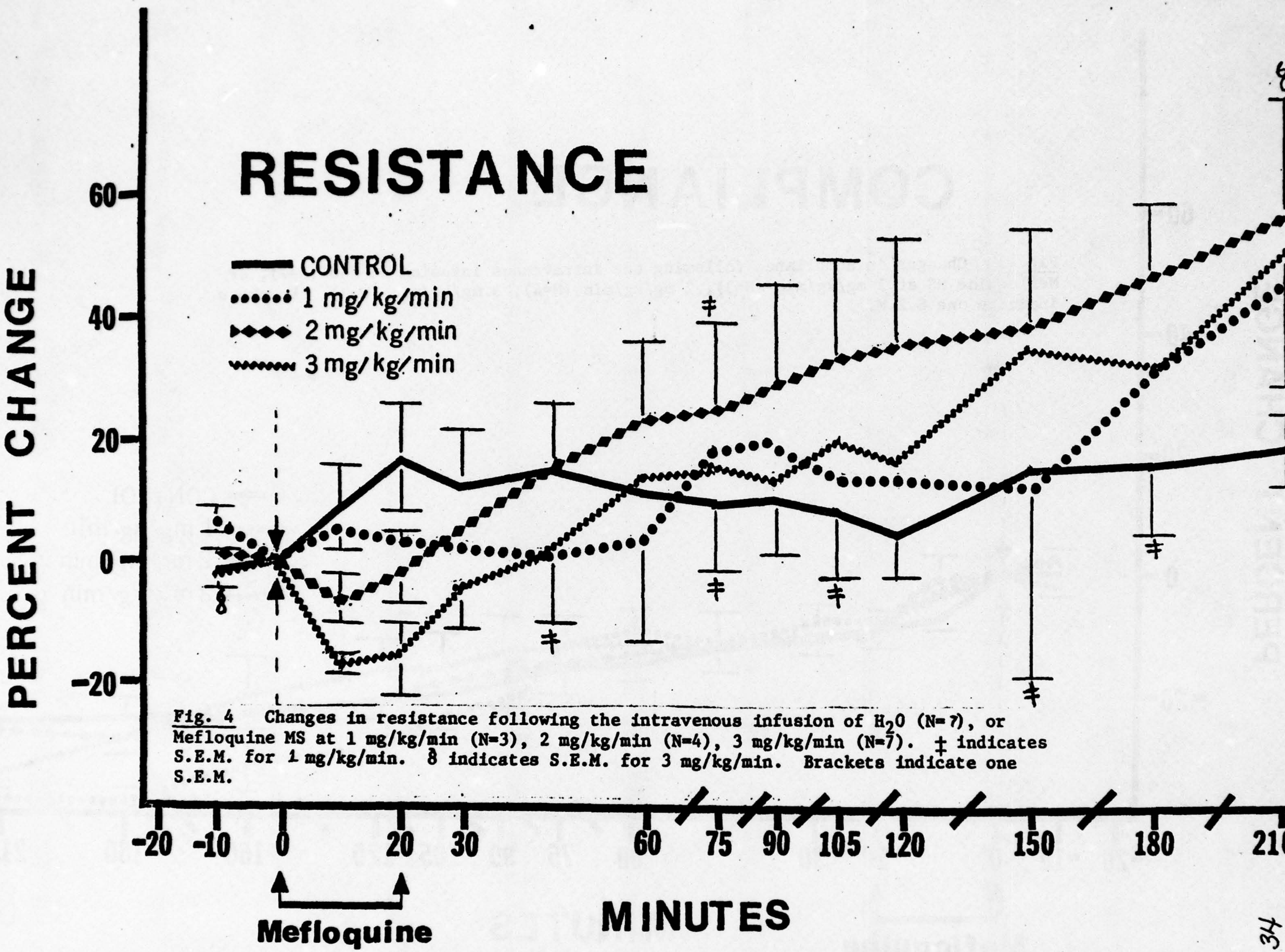


Fig. 3 Changes in compliance following the intravenous infusion of H_2O (N=7), or Mefloquine MS at 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), 3 mg/kg/min (N=7). Brackets indicate one S.E.M.



<u>Fig. 4</u> Changes in resistance following the intravenous infusion of H_2O (N=7), or Mefloquine MS at 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), 3 mg/kg/min (N=7). ‡ indicates S.E.M. for 1 mg/kg/min. 8 indicates S.E.M. for 3 mg/kg/min. Brackets indicate one S.E.M.

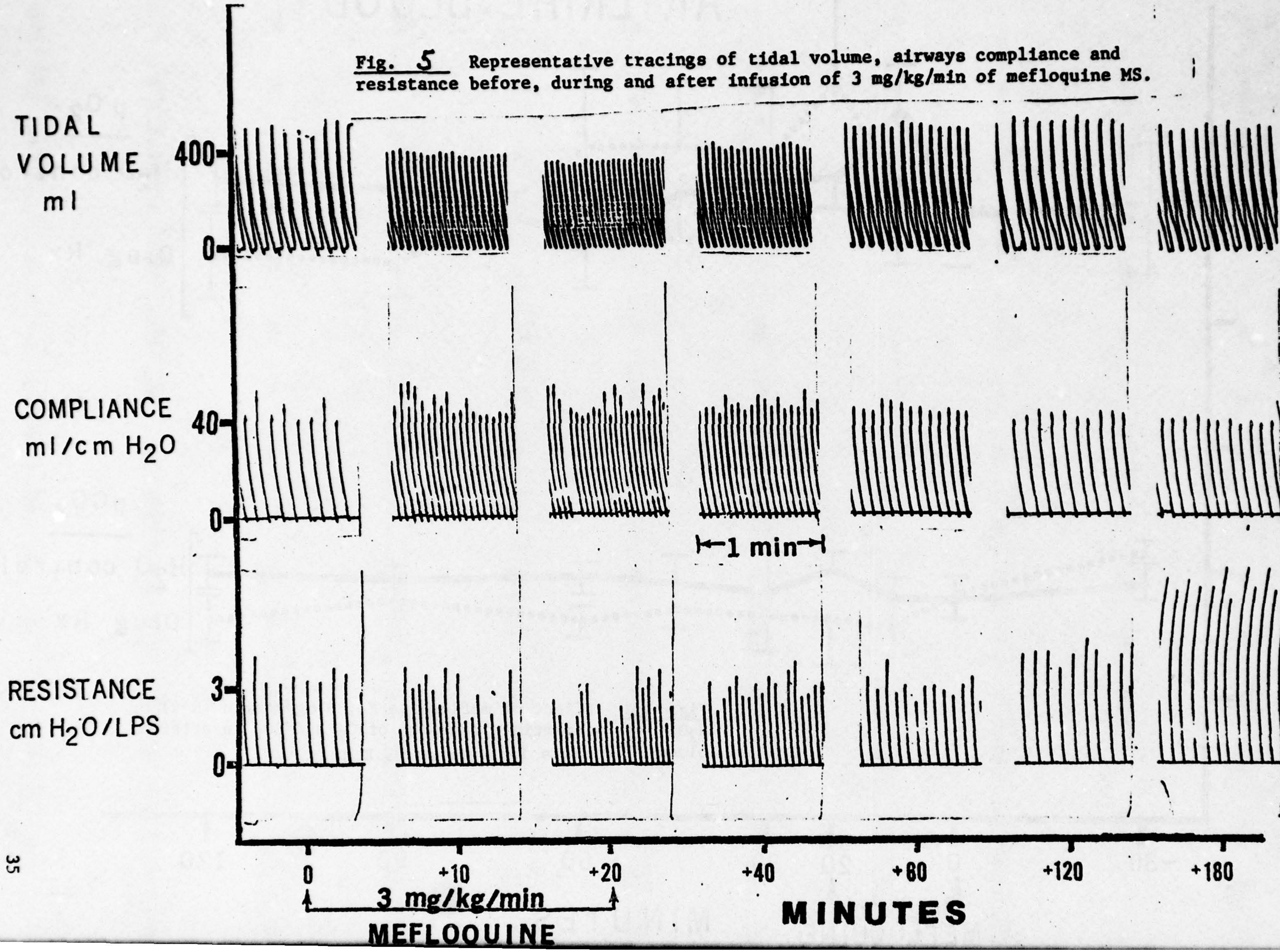


Fig. 5 Representative tracings of tidal volume, airways compliance and resistance before, during and after infusion of 3 mg/kg/min of mefloquine MS.

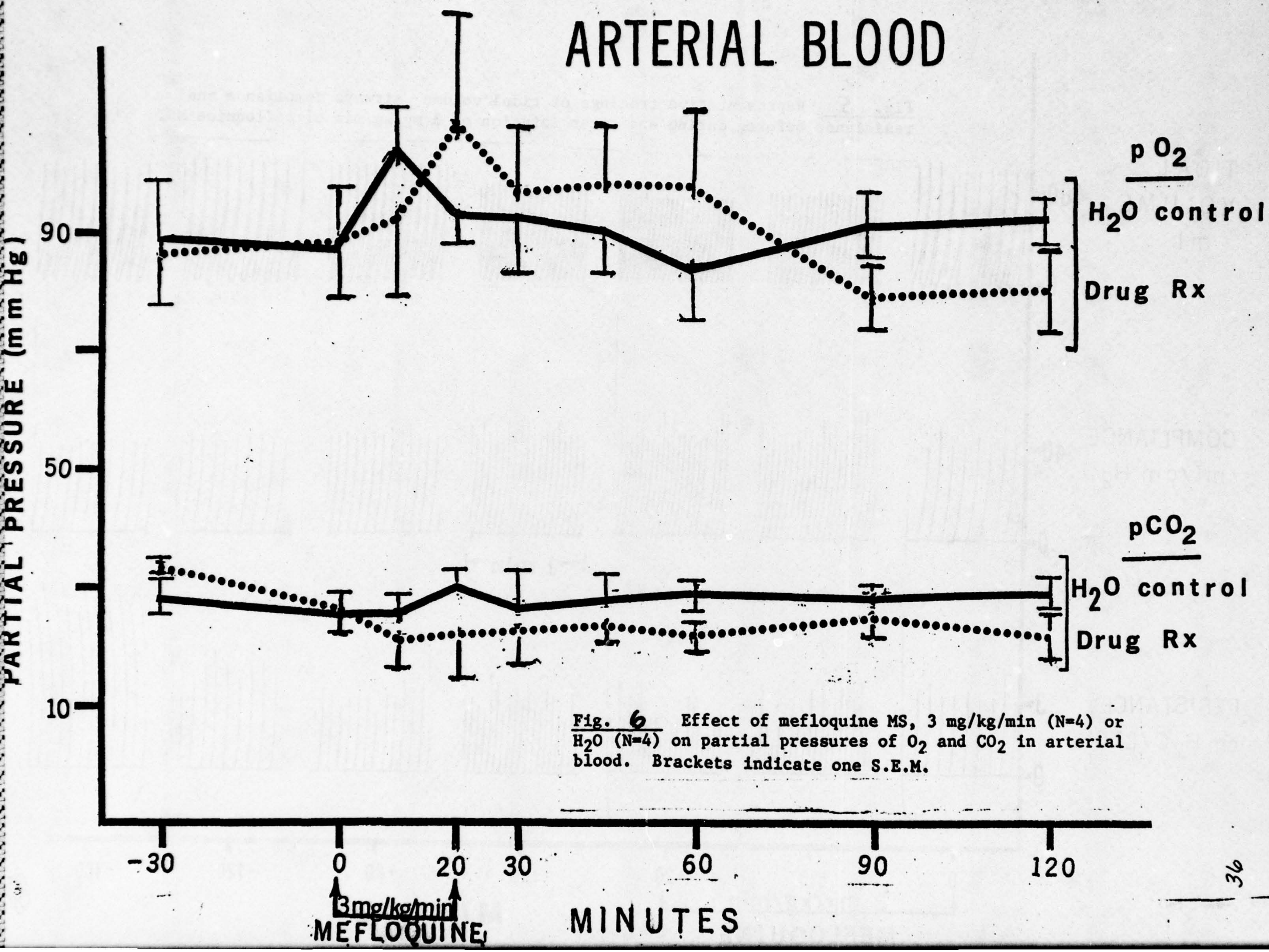


Fig. 6 Effect of mefloquine MS, 3 mg/kg/min (N=4) or H_2O (N=4) on partial pressures of O_2 and CO_2 in arterial blood. Brackets indicate one S.E.M.

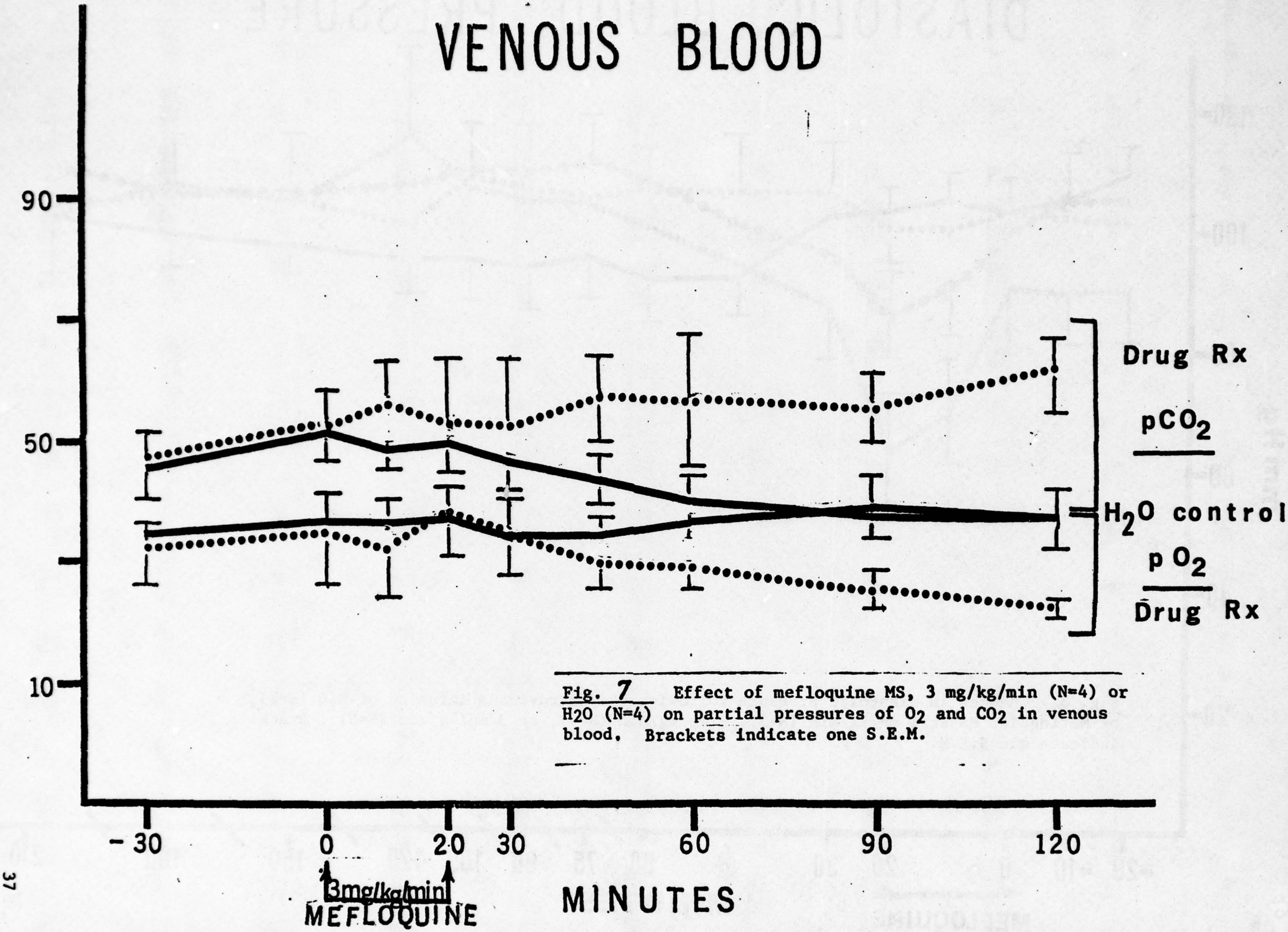


Fig. 7 Effect of mefloquine MS, 3 mg/kg/min (N=4) or H_2O (N=4) on partial pressures of O_2 and CO_2 in venous blood. Brackets indicate one S.E.M.

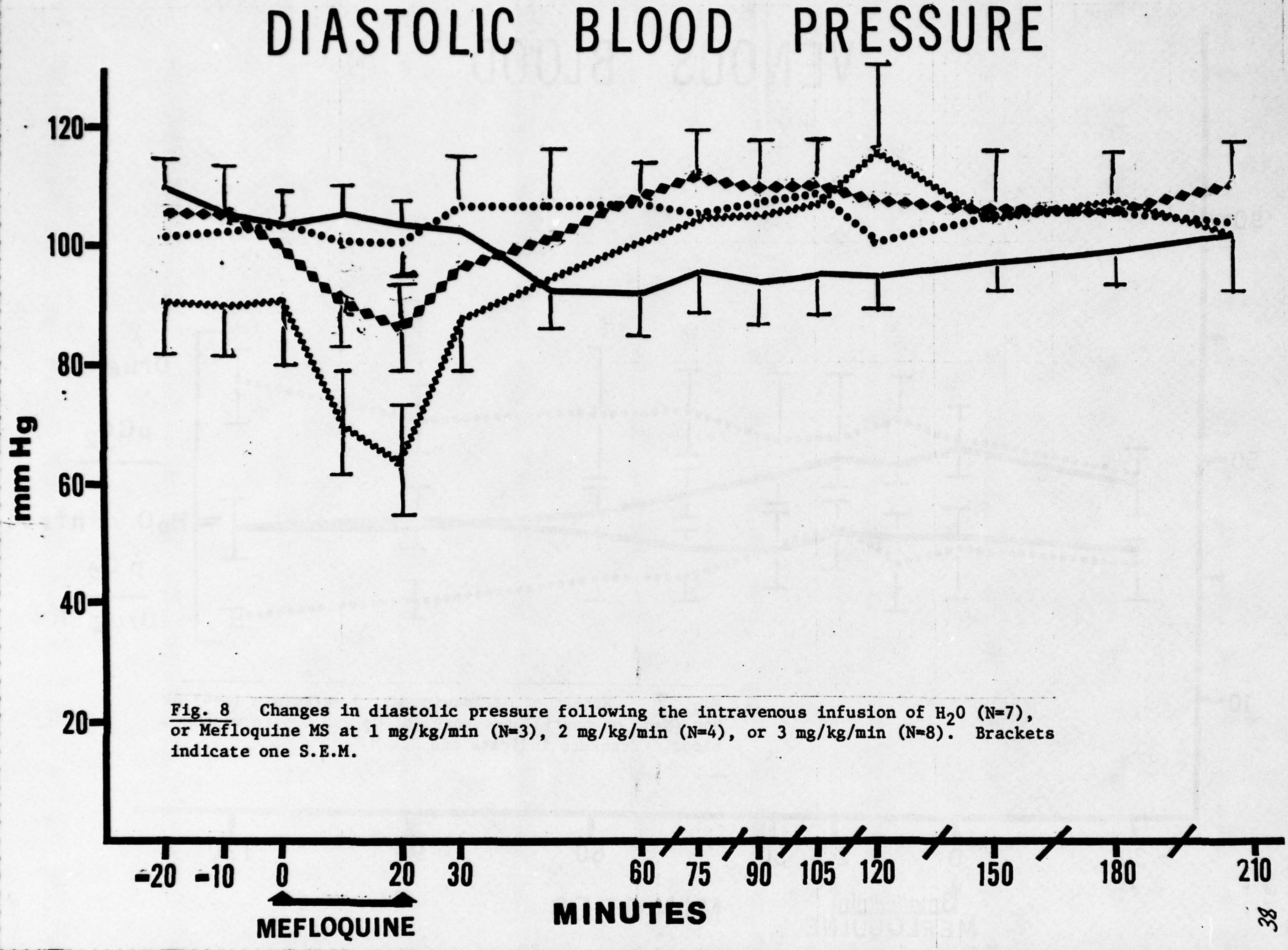


Fig. 8 Changes in diastolic pressure following the intravenous infusion of H_2O (N=7), or Mefloquine MS at 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=8). Brackets indicate one S.E.M.

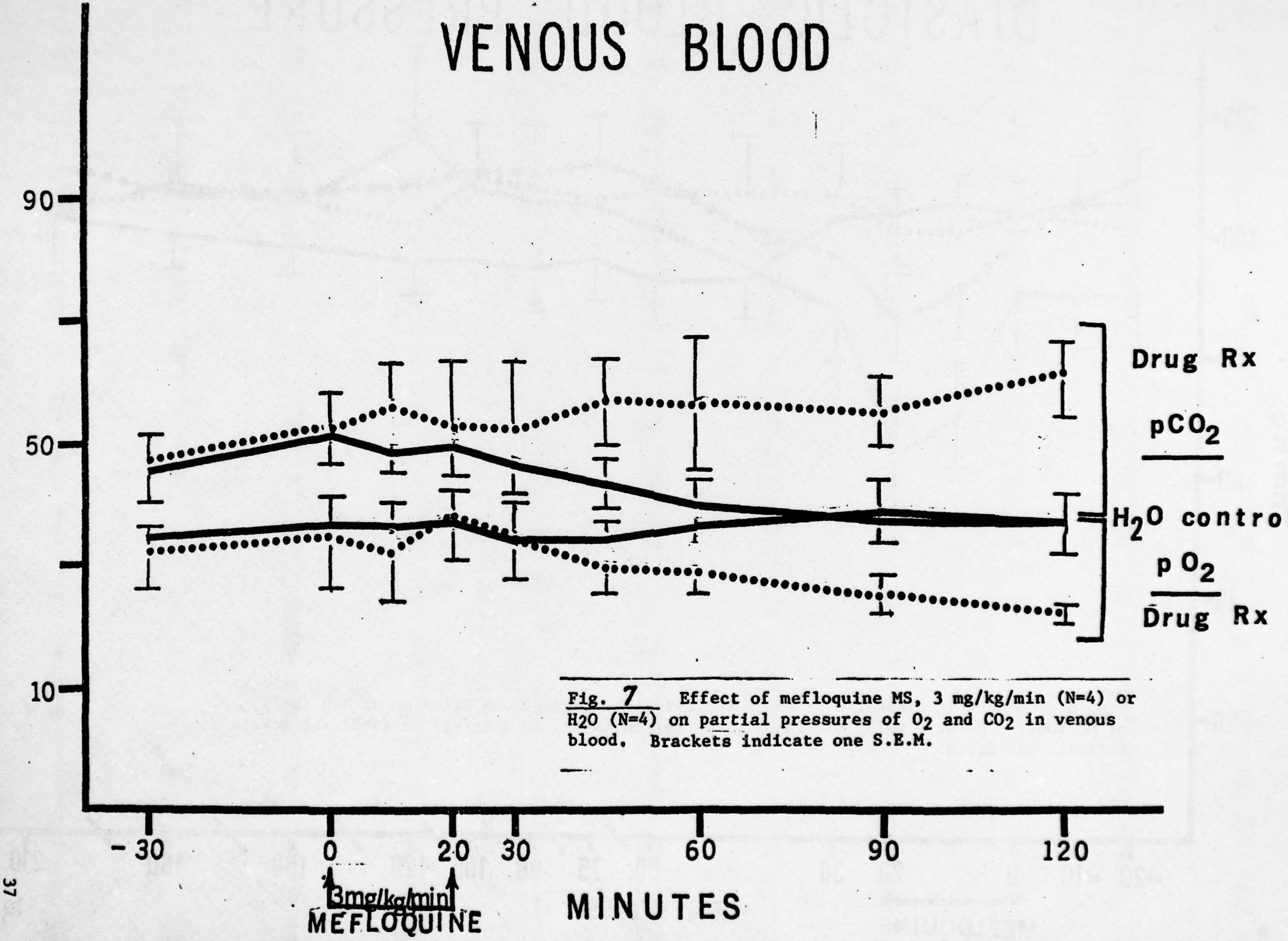


Fig. 7 Effect of mefloquine MS, 3 mg/kg/min (N=4) or H_2O (N=4) on partial pressures of O_2 and CO_2 in venous blood. Brackets indicate one S.E.M.

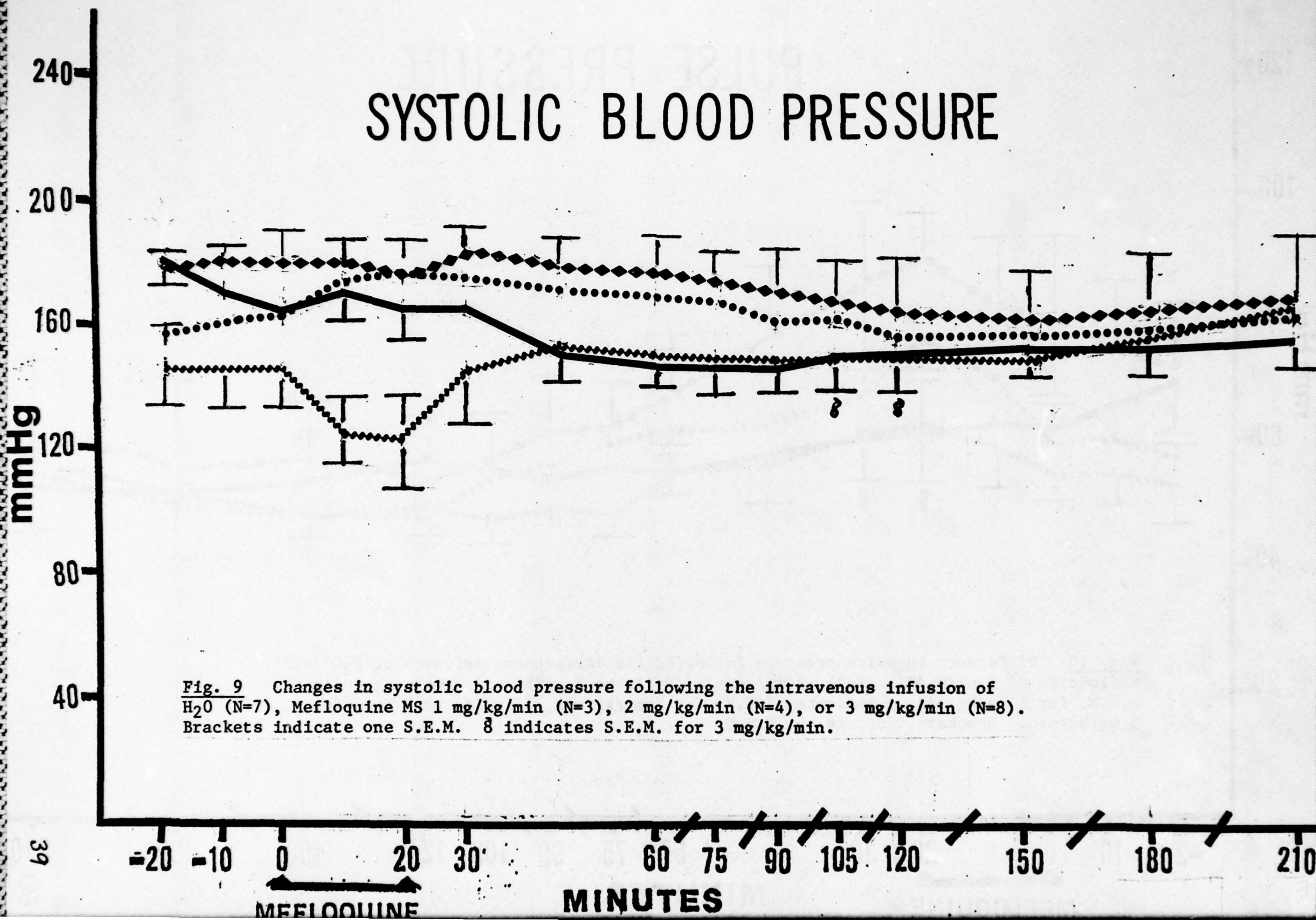
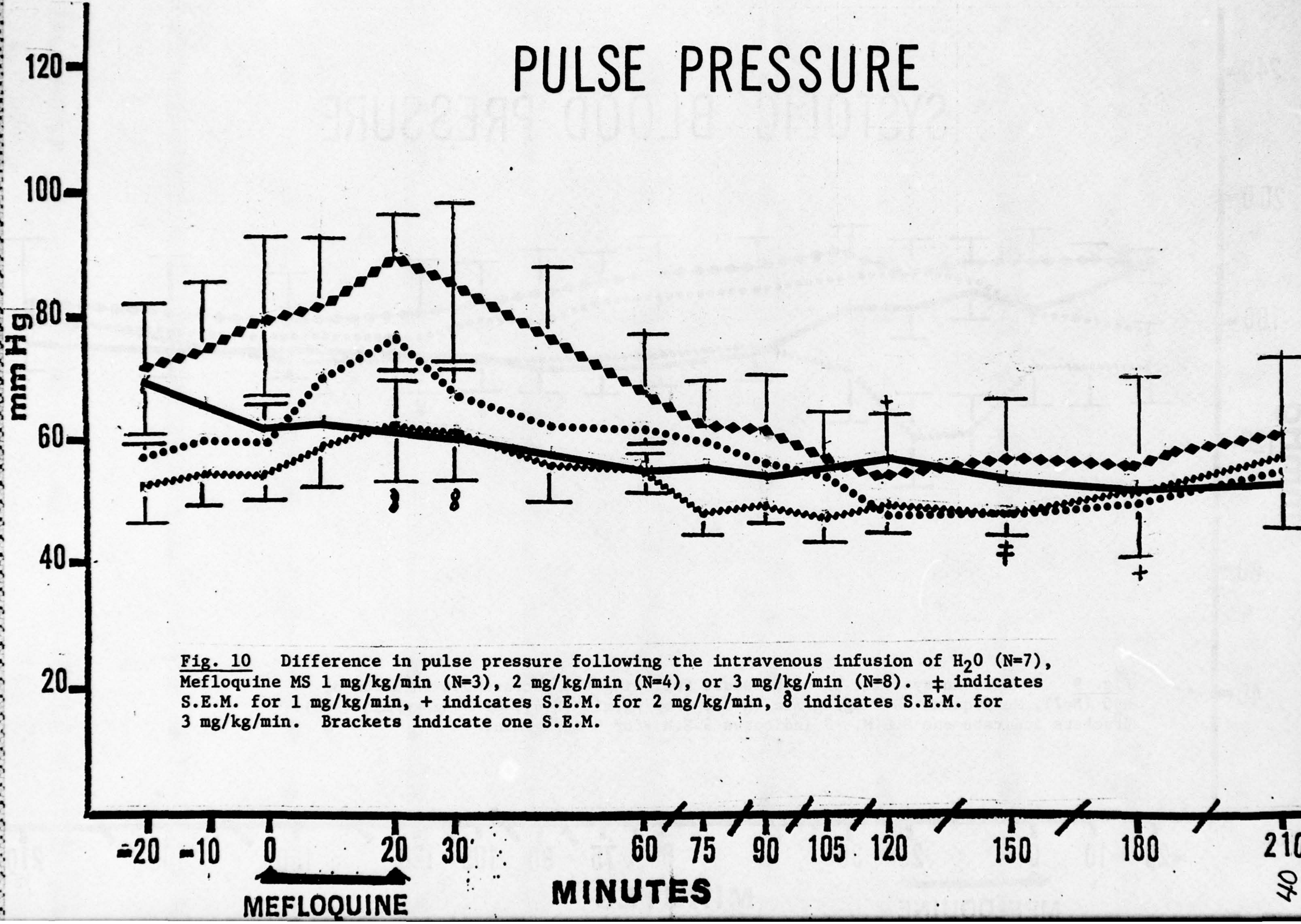


Fig. 9 Changes in systolic blood pressure following the intravenous infusion of H_2O (N=7), Mefloquine MS 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=8). Brackets indicate one S.E.M. 8 indicates S.E.M. for 3 mg/kg/min.



<u>Fig. 10</u> Difference in pulse pressure following the intravenous infusion of H_2O (N=7), Mefloquine MS 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=8). ‡ indicates S.E.M. for 1 mg/kg/min, + indicates S.E.M. for 2 mg/kg/min, 8 indicates S.E.M. for 3 mg/kg/min. Brackets indicate one S.E.M.

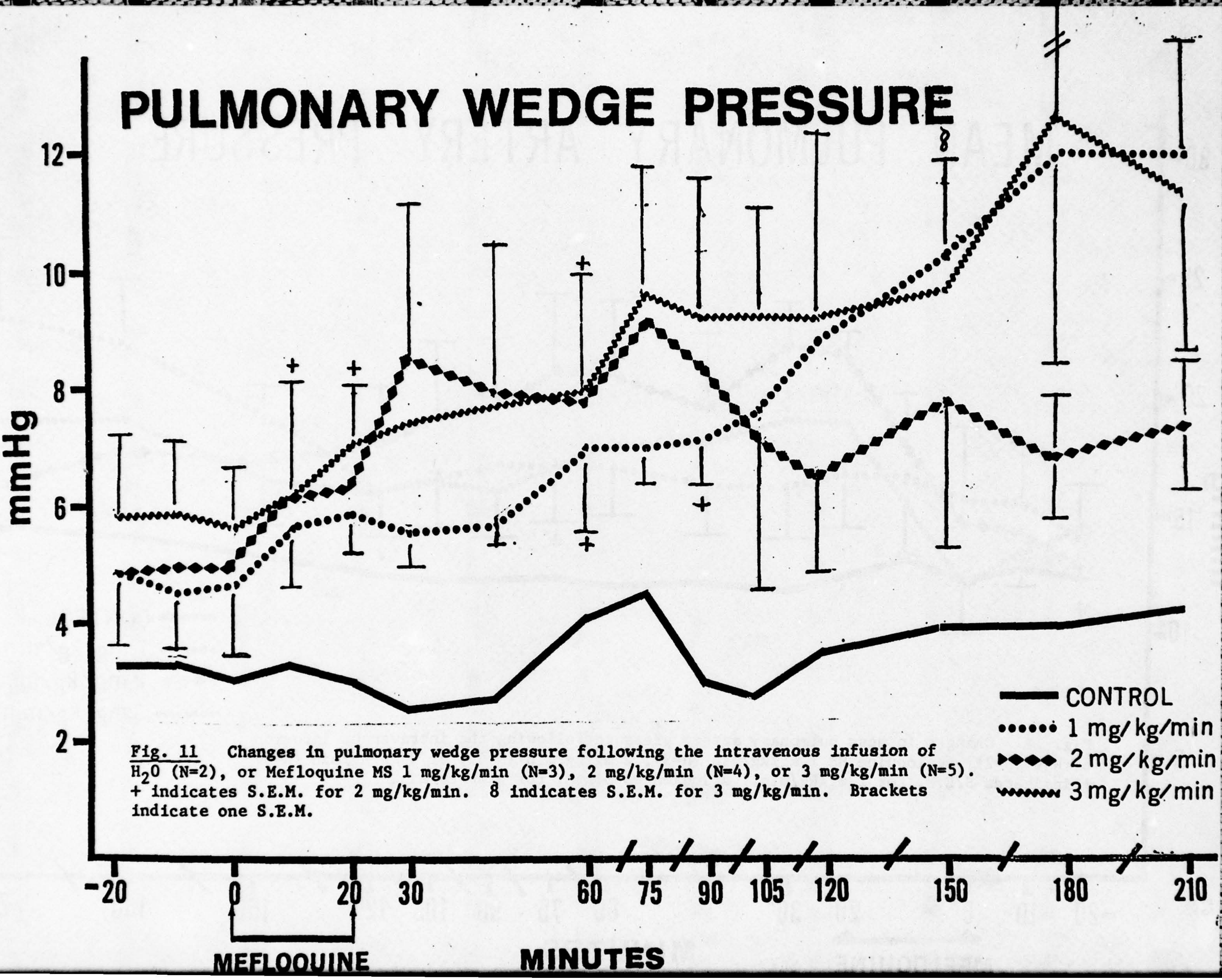


Fig. 11 Changes in pulmonary wedge pressure following the intravenous infusion of H_2O (N=2), or Mefloquine MS 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=5). + indicates S.E.M. for 2 mg/kg/min. 8̂ indicates S.E.M. for 3 mg/kg/min. Brackets indicate one S.E.M.

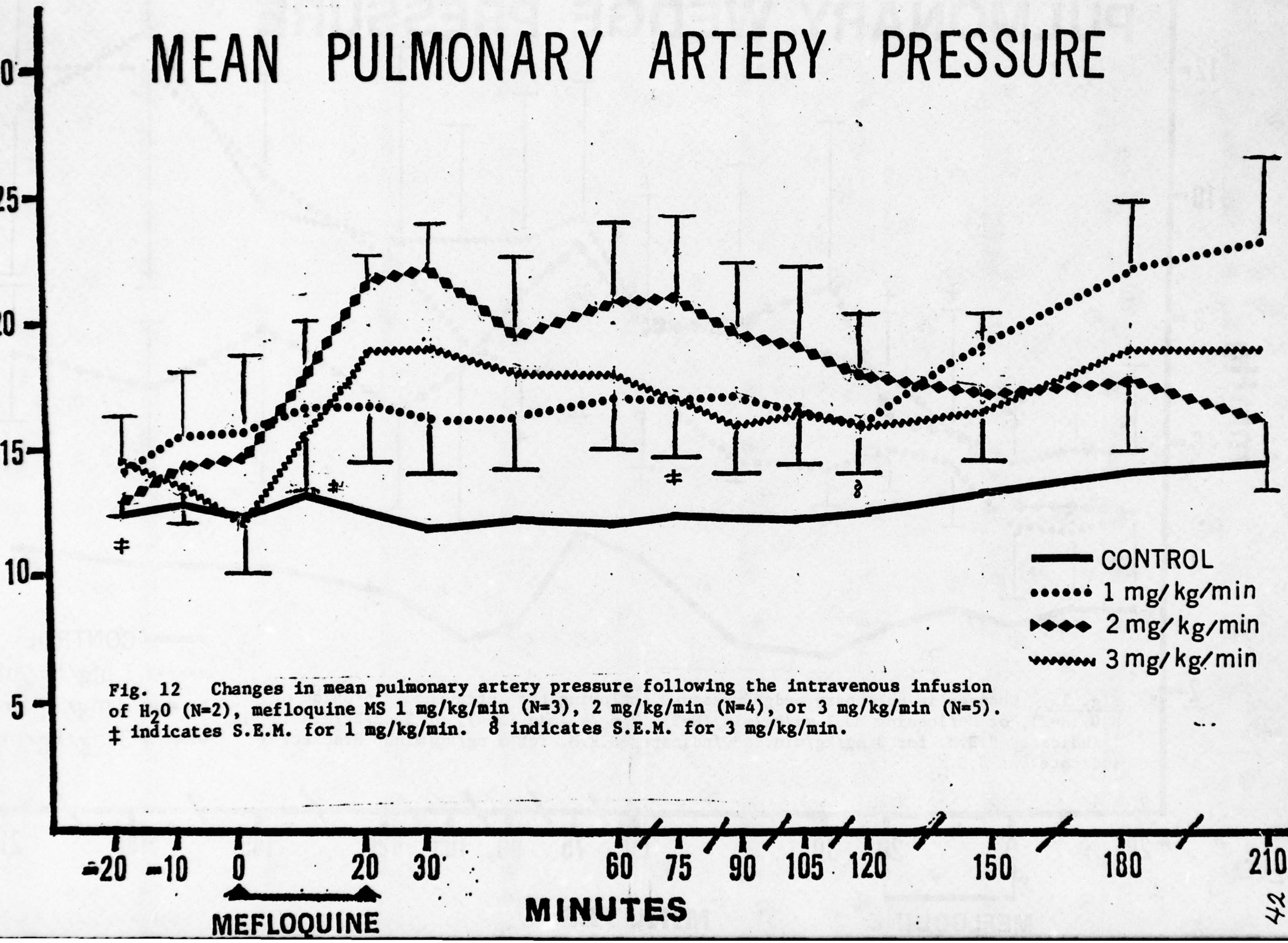


Fig. 12 Changes in mean pulmonary artery pressure following the intravenous infusion of H_2O (N=2), mefloquine MS 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=5). ‡ indicates S.E.M. for 1 mg/kg/min. ∂ indicates S.E.M. for 3 mg/kg/min.

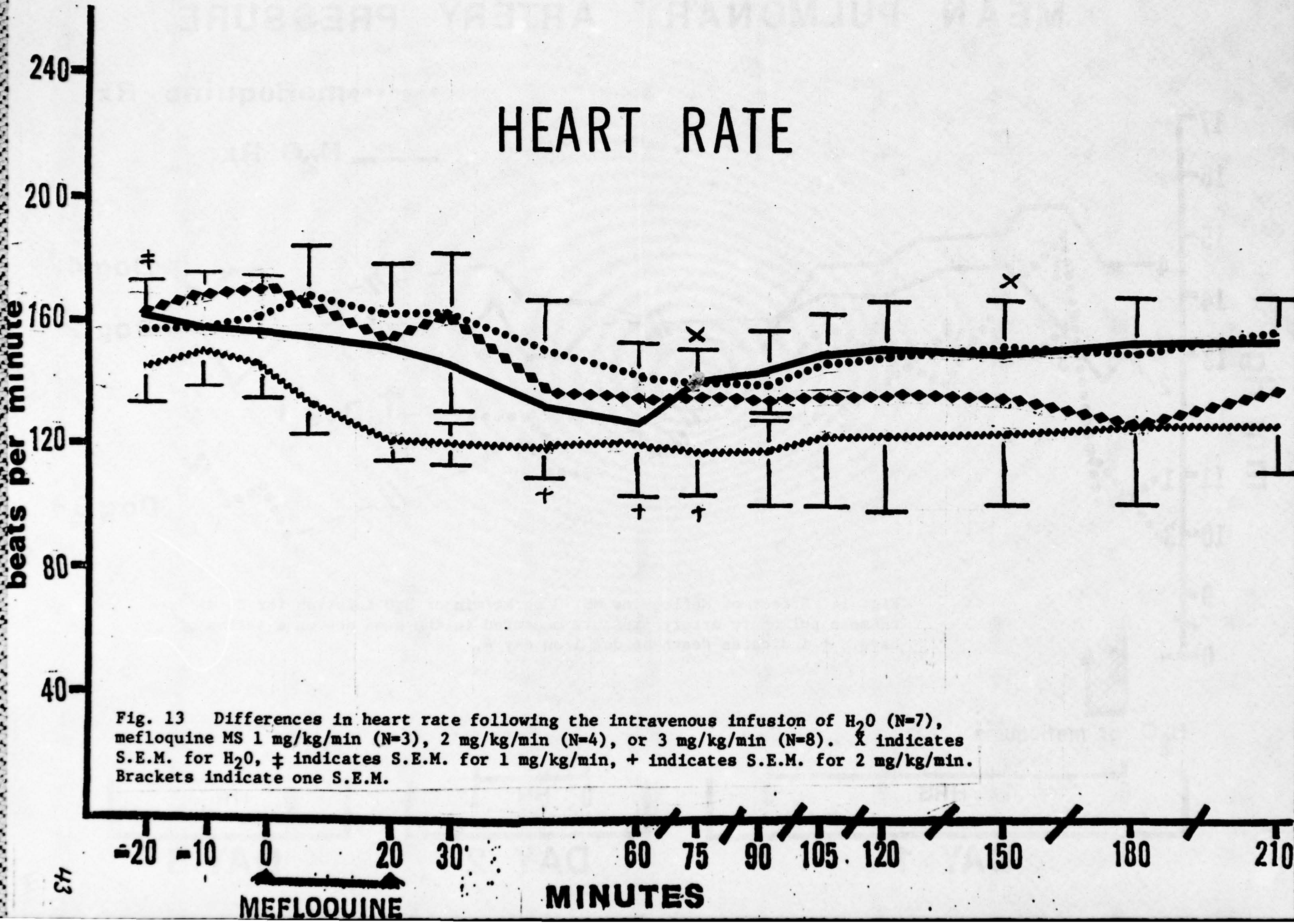


Fig. 13 Differences in heart rate following the intravenous infusion of H_2O (N=7), mefloquine MS 1 mg/kg/min (N=3), 2 mg/kg/min (N=4), or 3 mg/kg/min (N=8). X indicates S.E.M. for H_2O, ‡ indicates S.E.M. for 1 mg/kg/min, + indicates S.E.M. for 2 mg/kg/min. Brackets indicate one S.E.M.

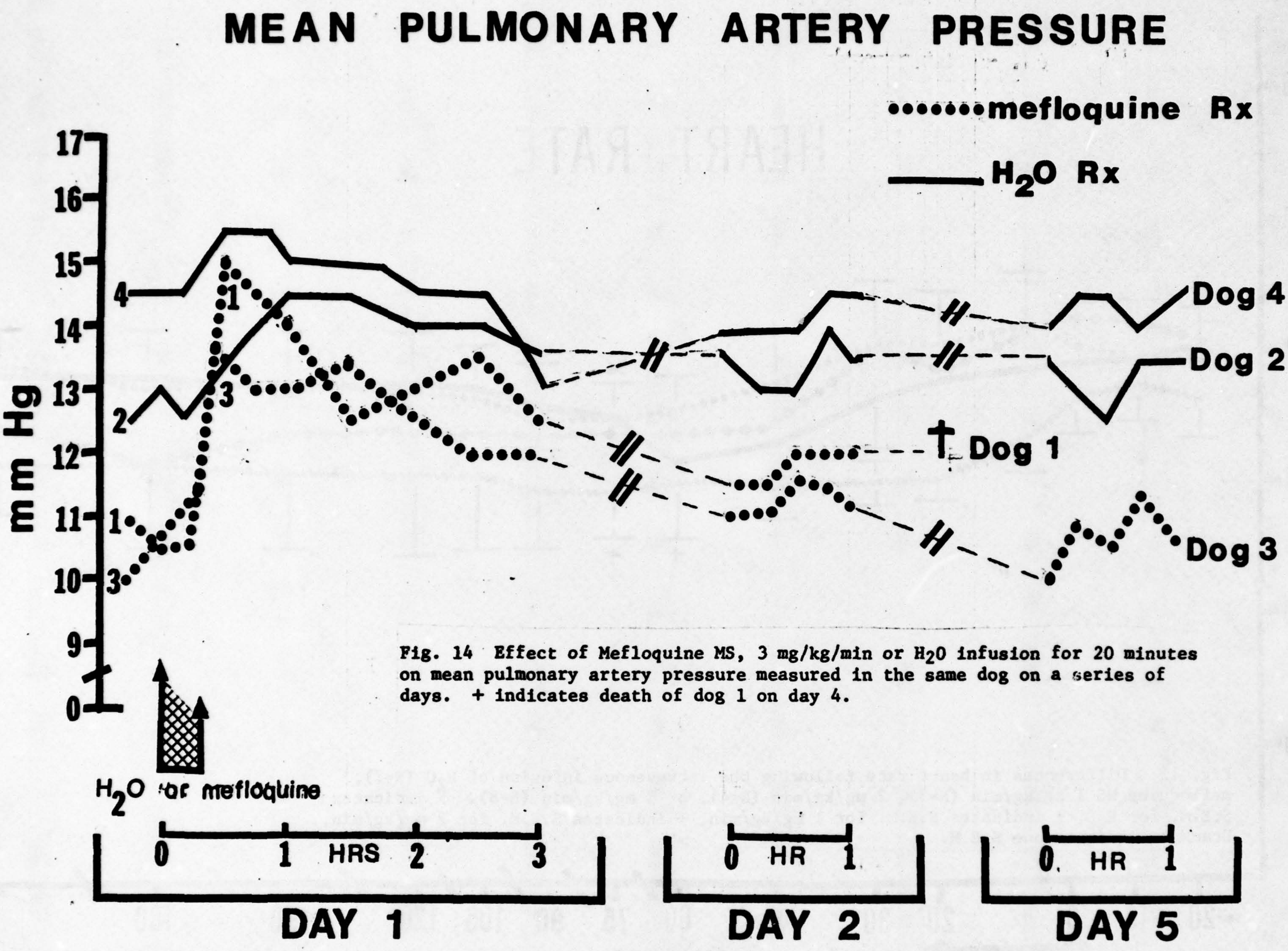


Fig. 14 Effect of Mefloquine MS, 3 mg/kg/min or H_2O infusion for 20 minutes on mean pulmonary artery pressure measured in the same dog on a series of days. + indicates death of dog 1 on day 4.

PULMONARY WEDGE PRESSURE

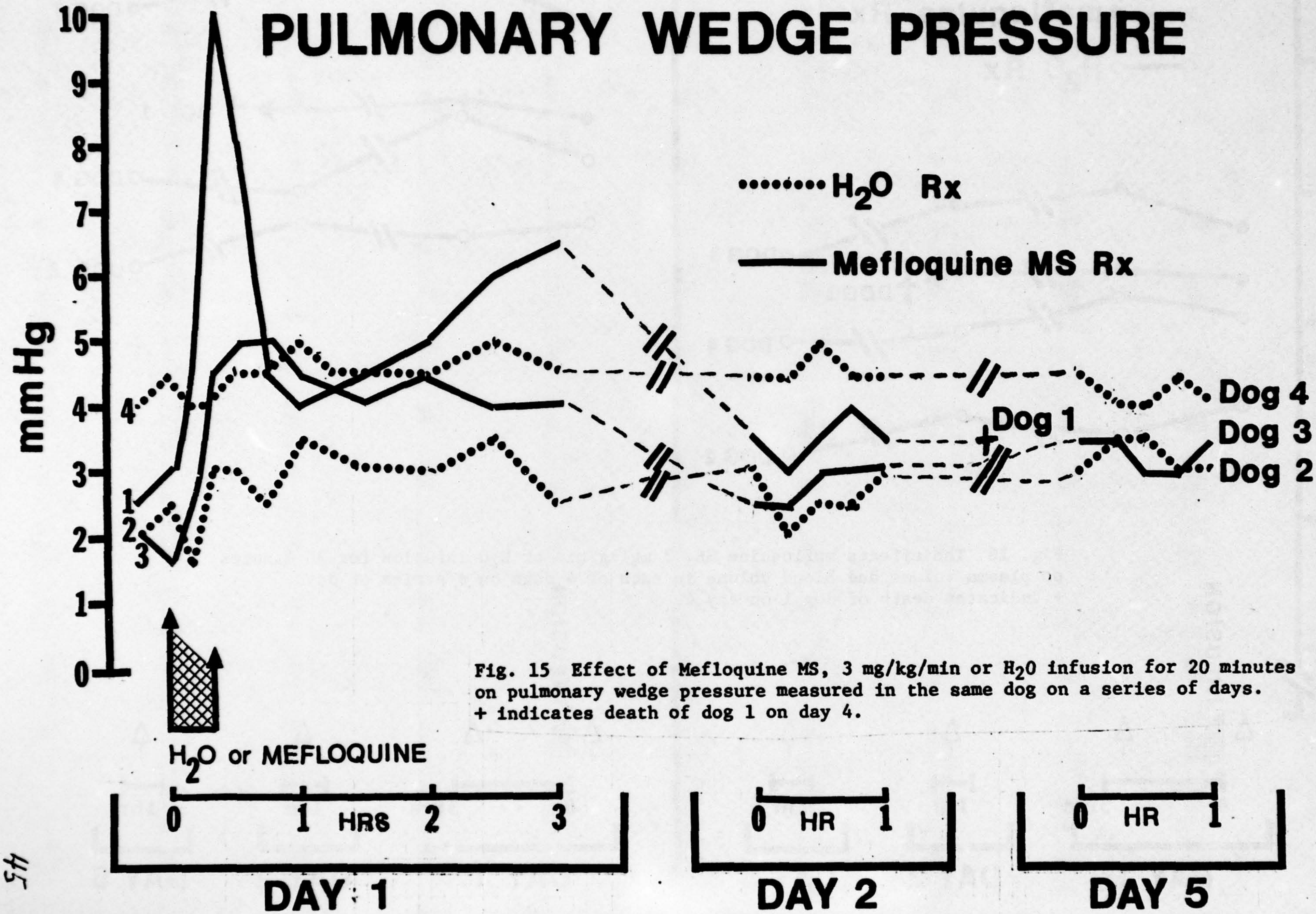


Fig. 15 Effect of Mefloquine MS, 3 mg/kg/min or H_2O infusion for 20 minutes on pulmonary wedge pressure measured in the same dog on a series of days. + indicates death of dog 1 on day 4.

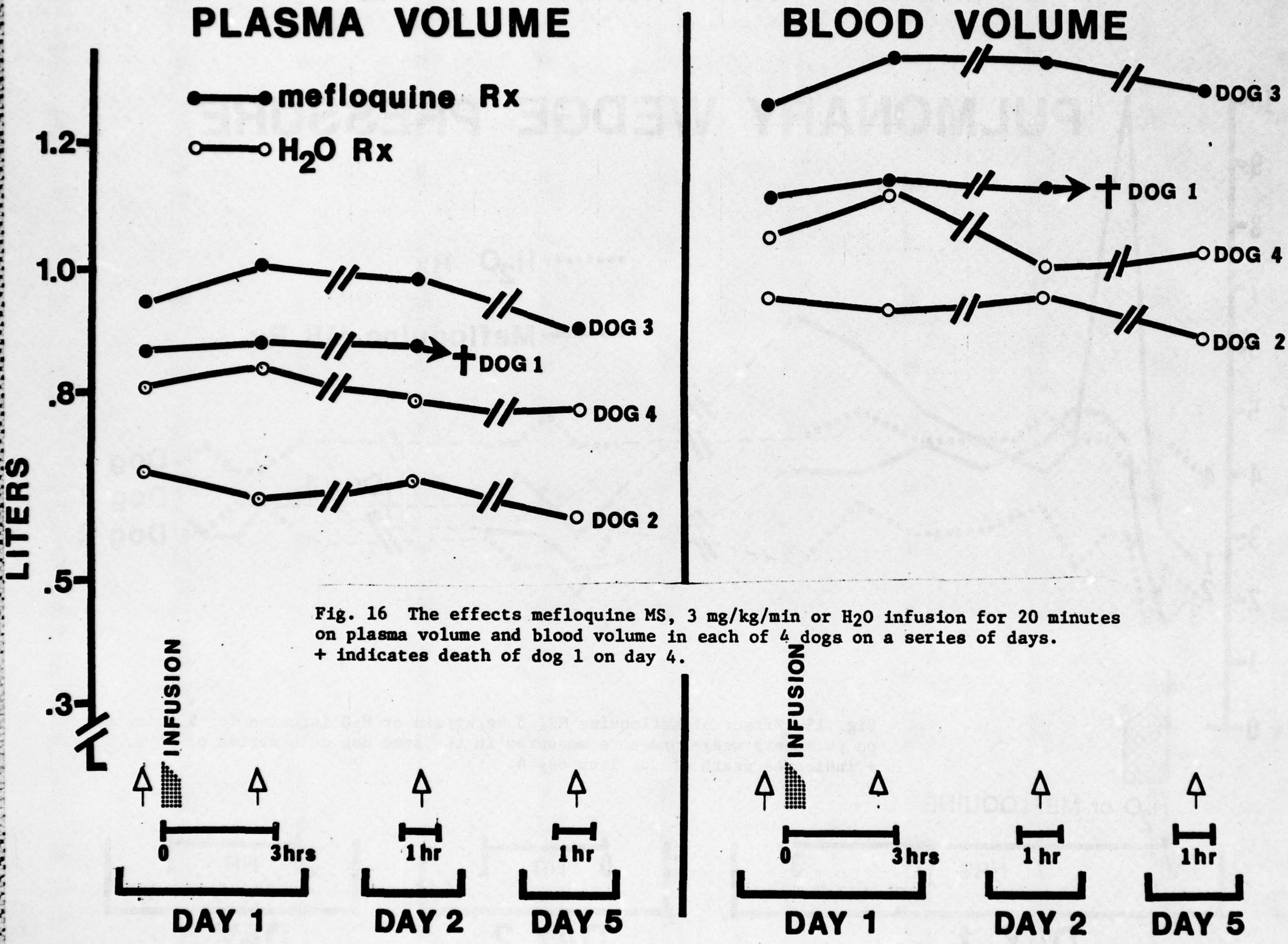


Fig. 16 The effects mefloquine MS, 3 mg/kg/min or H_2O infusion for 20 minutes on plasma volume and blood volume in each of 4 dogs on a series of days. + indicates death of dog 1 on day 4.

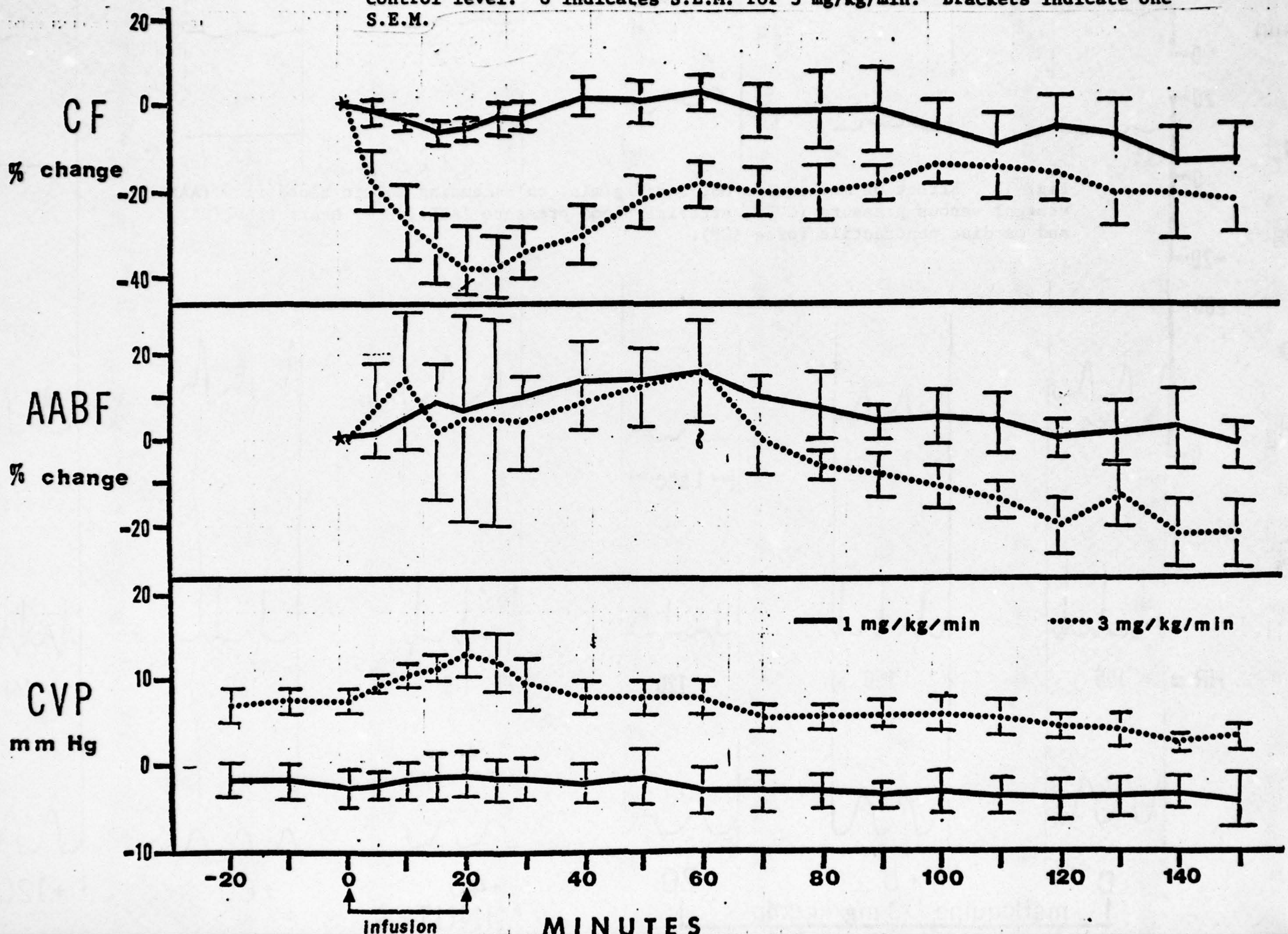


Fig. 17 Changes in cardiac contractile force (CF), ascending aortic blood flow (AABF), and central venous pressure (CVP) following the intravenous infusion of mefloquine MS 1 mg/kg/min (N=5) or 3 mg/kg/min (N=5). ★ indicates control level. ♁ indicates S.E.M. for 3 mg/kg/min. Brackets indicate one S.E.M.

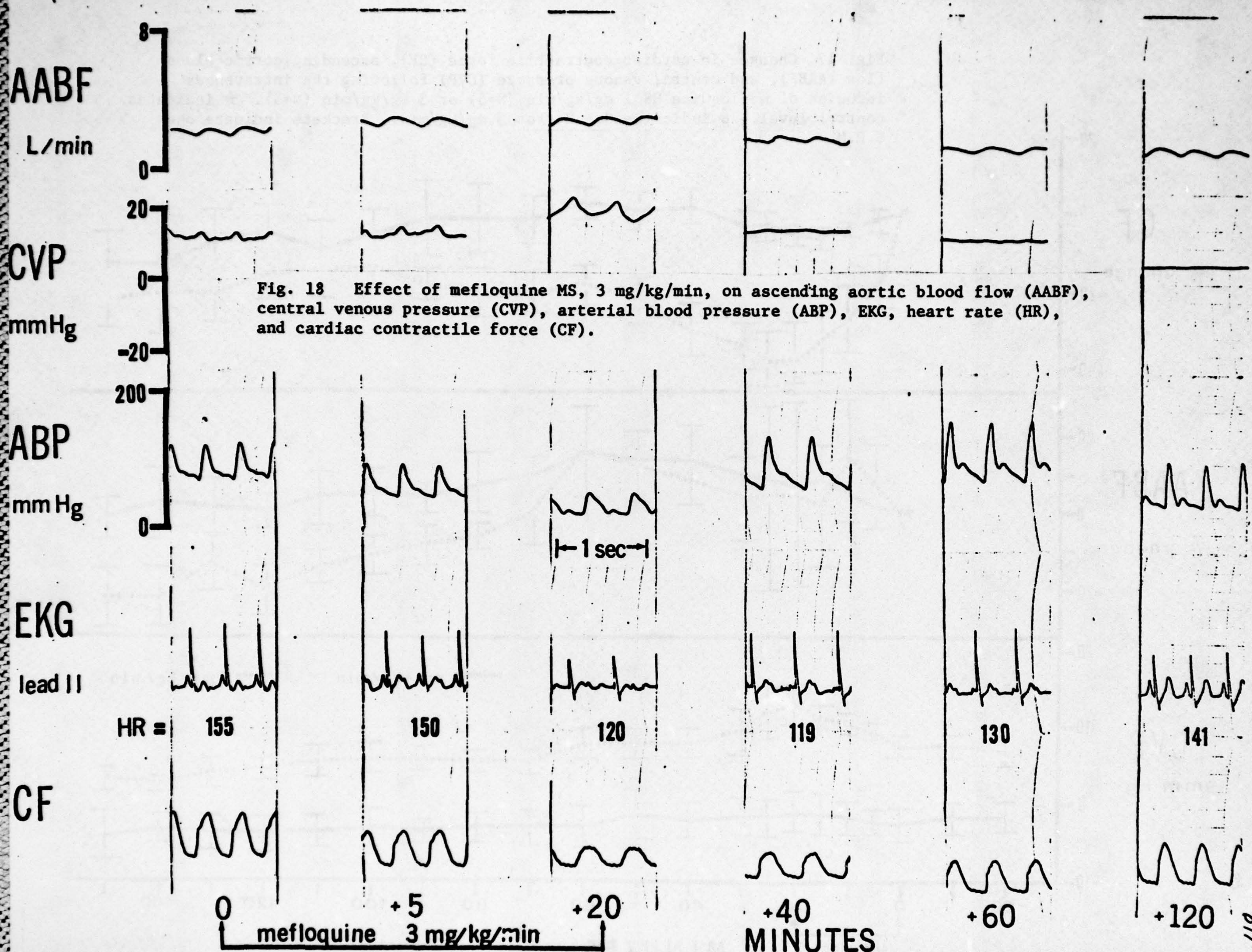


Fig. 18 Effect of mefloquine MS, 3 mg/kg/min, on ascending aortic blood flow (AABF), central venous pressure (CVP), arterial blood pressure (ABP), EKG, heart rate (HR), and cardiac contractile force (CF).

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April 23, 1976

Lewis C. Minor, Ph.D.
LTC. MSC
Department of Pharmacology
Walter Reed Army Institute of Research
Washington, DC 20012

RE: Cardiovascular and Pulmonary Effects of High dose-rate infusion of Mefloquine MS in dogs

Dear Lew:

The following is a summary letter report of several i.v. high-dose rate infusions of mefloquine methanesulfonate in dogs.

Background

Mefloquine methanesulfonate, or d,l erythro α-(2-piperidyl)-2,8 bis (trifluoromethyl)-4-quinolinemethanol methanesulfonate, is an antimalarial of single-dose curing potential. Extensive oral toxicity investigations in dogs and rodents have indicated certain dose regimens create lesions in the lymphoid tissue and liver (Lee et al., 1972, 1973, 1974). Moreover, acute intravenous administration in dogs has revealed acute cardio-respiratory involvement, hemoglobinuria and massive pulmonary edema in toxic and lethal doses (63-141 mg/kg), (Lee et al., 1975). This pulmonary edema and cessation of breathing has also been noted by Minor (WRAIR, personal communication, 1975) after about a total dose of 70 mg/kg when mefloquine was given as a rapid i.v. infusion of 10 mg/kg/min.

Purpose of Study

Previous animal work has demonstrated that mefloquine MS given at high doses-rates affects the pulmonary and cardiovascular systems. This short study was designed to elucidate the effects of acute high dose intravenous infusion of mefloquine methanesulfonate in dogs on pulmonary and cardiovascular function.

Drug

Mefloquine methanesulfonate (mefloquine MS) (bottle #BE 19191, Lot AL) was dissolved in 15% propylene glycol with deionized water to obtain a 20 mg/ml concentration for i.v. delivery. Alternately, the mefloquine MS was dissolved in 20% ethanol with deionized water to obtain a 20 mg/ml concentration. Infusion rates of from 3.6 to 4.9 ml/min were used in these experiments.

Animals

The animals used in this study were mongrel dogs of either sex and ranged in weight from 10 to 13 kg. Dogs with evidence of respiratory disease or other disease were excluded from the study.

Methods

Seven dogs were anesthetized with pentobarbital sodium, 30 mg/kg i.v. A stable level of anesthesia was maintained throughout the experiment with supplemental doses of pentobarbital sodium, 1.5 mg/kg s.q. every 20 minutes starting one hour after the initial dose.

For the measurement of arterial blood pressure and the introduction of drug solutions, a femoral artery and vein were cannulated in all dogs. A Swan-Ganz catheter was advanced through the right jugular vein, the right heart and into the pulmonary artery. Upon full inflation of a balloon on the tip of this catheter, pulmonary wedge pressure, which is an assessment of the left atrial pressure, was obtained. Balloon inflation for wedge pressure measurement was performed not more frequently than every 10 minutes and lasted for 5-10 seconds to preclude possible pulmonary infarction.

For the measurement of intra pleural pressure, the tip of a spear-shaped catheter was inserted through the left fifth intercostal into the pleural cavity and the shaft firmly secured to the skin and the incision made airtight with suture. An endotracheal tube with a side arm was connected directly to a mesh screen Fleisch pneumotachograph and the pressure difference across the screen was measured by a differential pressure transducer. This signal when calibrated corresponded to tidal airflow and in turn when integrated was also recorded as tidal volume. The pressure difference between the trachea and intrapleural space (transpulmonary pressure) was measured by a second differential pressure transducer.

Respiratory dynamic resistance and compliance were computed by introduction of the above electrical signals into a Buxco Electronics Pulmonary Mechanics Computer. This on-line analog computer performed necessary calculation after each breath and gave resistance and compliance signals which were displayed on a Grass polygraph. The basic method was described by Giles et al. (1971). Previous calibration of this computer with known flow and pressure signals provided a calibration standard for tidal volume, resistance and compliance.

RESULTS

Toxic infusion rates

Several high dose-rate infusions of mefloquine MS were performed to determine how this drug would be tolerated by the anesthetized dog. Figure 1 shows the effects of 10 mg/kg/min of mefloquine MS dissolved in 15% propylene glycol and water given at the volume rate of 4.9 ml/min. Respiration ceased

after a total dose of 70 mg/kg with cardiac action ceasing after about 80 mg/kg. Two other dogs also died and demonstrated respiratory and then cardiac arrest at doses of between 65 and 80 mg/kg. One of these dogs exhibited a Cheyne-Stokes type of respiration halfway through the infusion. Other lower dose-rates were tested using the same solvent system. Two additional dogs were given an infusion dose-rate of 8 mg/kg/min; one died after a total dose of 70 mg/kg and the other survived a total dose of 100 mg/kg. Neither of two other dogs died during an infusion rate of 6 mg/kg or a total dose of 100 mg/kg.

When ethanol was used to enhance mefloquine MS water solubility instead of propylene glycol, death occurred with a lower dose-rate. Both of the dogs given mefloquine MS dissolved in 20% ethanol and water infused in volume rates of 3.6 or 4.9 and dose rates of 10 mg/kg/min died after total doses of only 40 and 50 mg/kg and both exhibited a Cheyne-Stokes types pattern of respiration. The vehicle itself given at these volume rates did produce a slight hypotension, bradycardia and tachypnea but was certainly not lethal. Gross examination of the lungs and airways of all spontaneously breathing dogs which died during the infusion of mefloquine MS revealed evidence of pulmonary edema and small areas of hemmorrhage both on the surface of the lung and within the lung.

One additional dog, artifically respired with positive pressure ventilation, was additionally prepared with a Walton-Brodie strain gauge arch on the right ventricle and a electromagnetic flow probe around the ascending aorta. Infusion of 10 mg/kg/min of Mefloquine MS dissolved in propylene glycol did not produce death until a total dose of 95 mg/kg had been delivered (figure 2). This death was due to cardiovascular failure.

Discussion

High dose-rate infusions of mefloquine MS of 10 mg/kg/min route produced a dramatic drop in blood pressure, heart rate and tidal volume and equally marked elevations in respiratory rate and pulmonary artery pressure. Pulmonary wedge pressure was also slightly elevated. Pulmonary compliance and resistance could not be accurately assessed during much of the drug infusion because of the marked reduction of tidal volume, but compliance appeared to increase slightly before death while the immediate effects of this infusion dose-rate on resistance was a reduction. While both the respiratory and cardiovascular systems failed and appeared to be involved in the death of the animal, cessation of breathing appeared to occur first. A Cheyne-Stokes breathing pattern (a crescendo-decrescendo pattern) was noted in severals of the spontaneously breathing high dose-rate dogs and may indicate depression of peripheral chemoreceptors with the only remaining negative feedback control system consisting of the CO_2 sensitive mechanism within the brain stem. Also possibly contributing to this breathing pattern is an increase in circulation time between the lung and the brain stem due

to cardiac depression produced by mefloquine MS. The pulmonary edema and focal areas of hemorrhage seen with the alcohol-water solvent system may be due to the physical precipitation of the mefloquine MS in the blood as the vehicle is diluted by the blood. This may result in mechanical blockade to blood flow in the very small pulmonary vessels. Certainly the elevation of central venous pressure could also be related to such an increase in resistance. In the artifically respired animal, respiration was mechanically maintained; therefore, the lethal dose 95 mg/kg was considerabley higher than that obtained in spontaneously breathing dogs and the lethal effect was due to the production of cardiovascular failure. High dose-rates of 8 to 10 mg/kg/min of mefloquine MS can be lethal to dogs (55 to 80 mg-total dose), with respiration ceasing before the cardiovascular system fails.

Sincerely yours,

Robert W. Caldwell

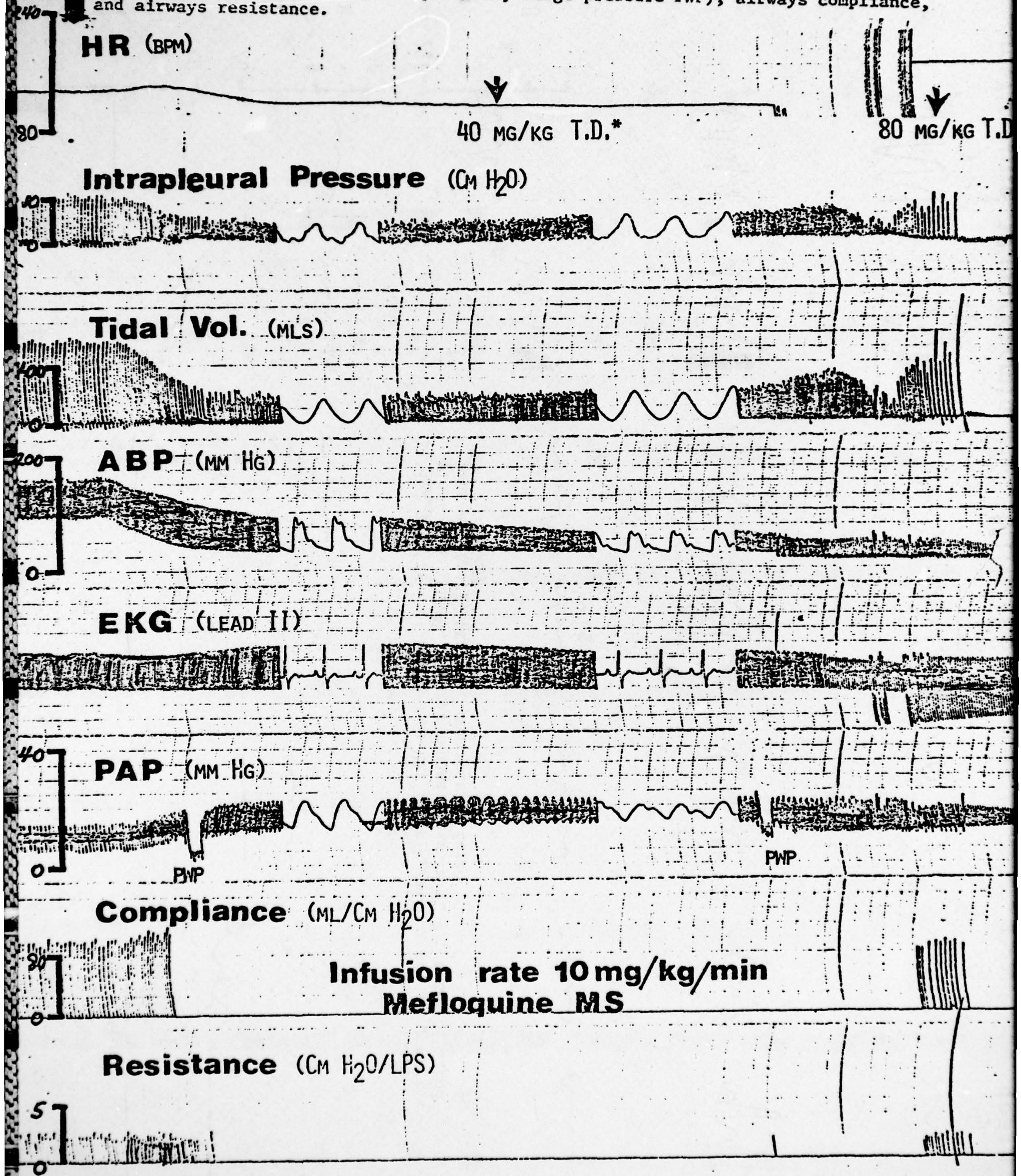
Robert W. Caldwell, Ph.D.
Associate Professor of Pharmacology

Clinton B. Nash

C. B. Nash, Ph.D.
Professor of Pharmacology

drm

Fig. 1 Effect of a toxic dose-rate 10 mg/kg/min of mefloquine MS on a heart rate, intrapleural pressure, tidal volume, arterial blood pressure, EKG, pulmonary artery pressure (with pulmonary wedge pressure-PWP), airways compliance, and airways resistance.



* T.D. - TOTAL DOSE

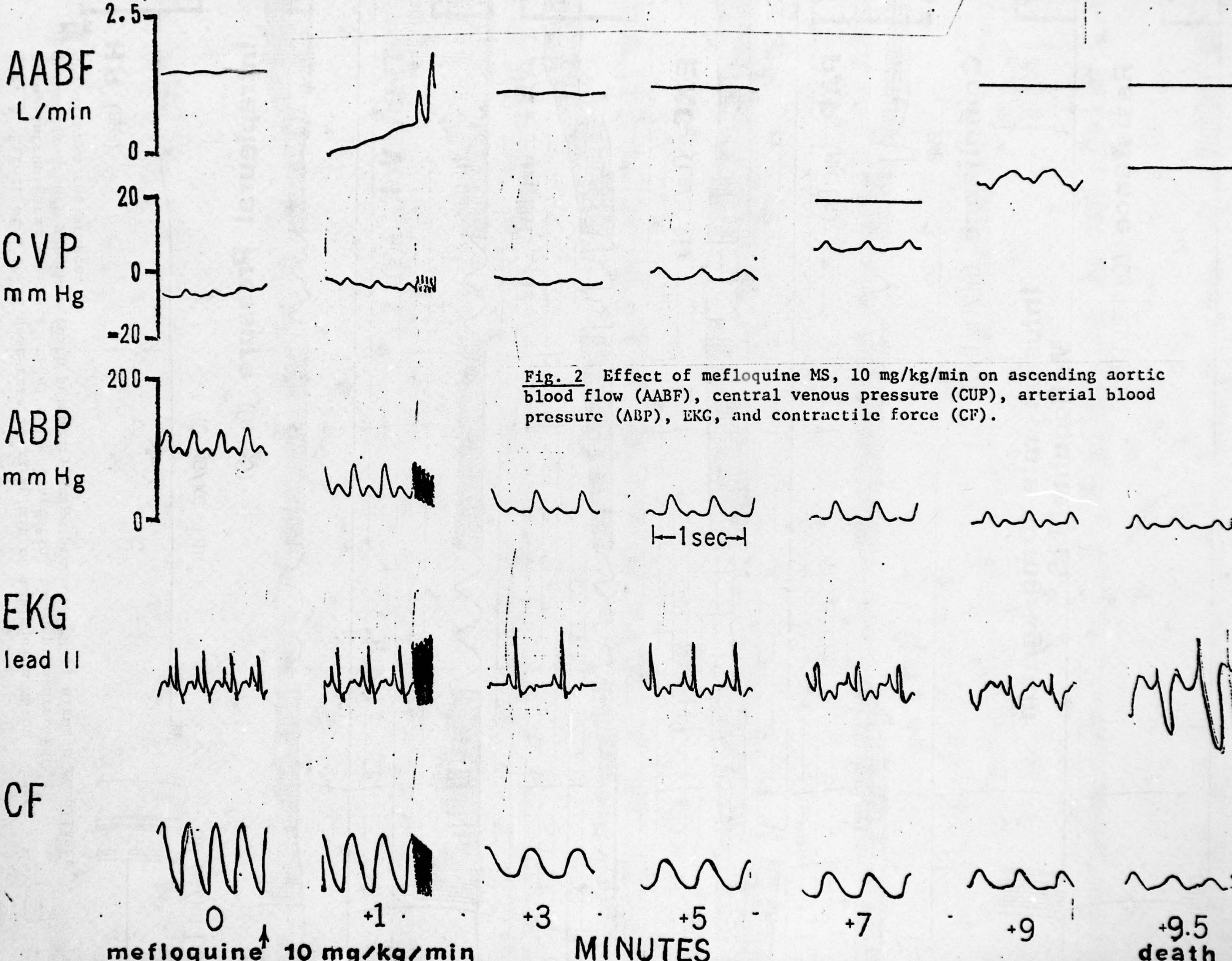


Fig. 2 Effect of mefloquine MS, 10 mg/kg/min on ascending aortic blood flow (AABF), central venous pressure (CUP), arterial blood pressure (ABP), EKG, and contractile force (CF).

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